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16. ABSTRACT

This document summarizes current scientific information regarding the effects of nickel on man and the environment. The observed effects, as presented herein, constitute the health basis from which the U. S. Environmental Protection Agency will make determinations regarding the possible listing and regulating of nickel as a hazardous air pollutant under the Clean Air Act. Specifically, this document discusses the following topics--physical and chemical properties of nickel; environmental distribution and cycling; nickel metabolism, toxicology and essentiality--and identifies the factors most germane to assessing quantitative human health risks.

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PREFACE

The Environmental Criteria and Assessment Office, in consultation with other Agency and non-Agency scientists, has prepared this health assessment to serve as a "source document" for Agency-wide use. Specifically, this document was prepared at the request of the Office of Air Quality Planning and Standards.

In the development of this assessment document, the scientific literature has been inventoried, key studies have been evaluated, and summary/conclusions have been prepared such that the toxicity of nickel is qualitatively identified. Observed effect levels and dose-response relationships are discussed where appropriate in order to place adverse health responses in perspective with observed environmental levels.

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1. INTRODUCTION

This document is concerned with the current data base for nickel toxicology most relevant for assessing associated human health risks and includes information on the metabolism of nickel as it relates to the expression of nickel toxicity or other aspects of potential regulatory concern. This document is not meant to be an exhaustive review of all available literature regarding the toxicity of nickel.

The second chapter of the document provides a concise summary of the information contained within the text of the report.

The third chapter provides background information, including discussion of: physical and chemical properties of nickel; the environmental cycling of nickel; and levels of nickel in various media, e.g. air, water, food and soil.

The fourth chapter is concerned with metabolism and includes information on absorption, distribution, excretion and conditions influencing nickel movement *in vivo*.

The fifth chapter dealing with nickel toxicology, is divided first into experimental and clinical data for a variety of adverse effects including carcinogenicity. The latter part is concerned with epidemiological studies reported mainly for nickel carcinogenicity and its role as a potent allergen.

There is growing evidence that nickel is an essential element in a number of animal species, and this may also be the case for man. Since this property necessitates that there be some minimal systemic intake of the element, data on nickel essentiality must be considered in any regulatory framework for exposure control and, therefore, this subject is discussed in the sixth chapter.

As indicated in the title, the report is selective in that the focus is on information most germane to assessing human health risks arising from nickel exposure. As such, the seventh chapter deals with the most pertinent information necessary for determining human health risk. This section addresses: (1) the aggregate human intake of nickel; (2) the dose-effect and dose-response relationship of nickel; (3) populations at risk; (4) current regulations and standards; and (5) a quantitative cancer risk assessment for exposure to nickel in the ambient air. This section calls upon information presented within the previous sections for its analyses of the human health risk to nickel.

Structurally, this report is based on several documents primarily prepared by the present authors for the U.S. Environmental Protection Agency including the Ambient Water Quality Criteria report for nickel. Information has been updated where appropriate.

2. SUMMARY AND CONCLUSIONS

2.1 BIOLOGICAL SIGNIFICANCE AND ADVERSE HEALTH EFFECTS OF NICKEL

2.1.1 Nickel Metabolism

Routes of nickel intake for man and animals are inhalation, ingestion and percutaneous absorption. Parenteral exposure is mainly of importance in experimental animal studies.

The relative amount of inhaled nickel which is absorbed from various compartments of the pulmonary tract is a function of both chemical and physical forms. Pulmonary absorption into the blood stream is probably greatest for nickel carbonyl vapor, with animal studies suggesting that about half of the inhaled amount is absorbed. Nickel in particulate matter is absorbed from the pulmonary tract to a considerably lesser degree than nickel carbonyl. Smaller particles are lodged deeper in the respiratory tract and the relative absorption is greater than with larger particles. Lung models and limited experimental data suggest several percent absorption. While insoluble nickel compounds may undergo limited absorption from the respiratory tract, their relative insolubility may have implications for the carcinogenic character of nickel, as will be noted below.

Absorption from the gastrointestinal tract of dietary nickel is on the order of one to ten percent in man and animals from both foodstuffs and beverages.

Percutaneous absorption of nickel occurs and is related to nickel-induced hypersensitivity and skin disorders. The extent to which nickel enters the bloodstream by way of the skin cannot be stated at the present time.

Absorbed nickel is carried by the blood, although the extent of partitioning between erythrocyte and plasma cannot be precisely stated. In any event, plasma or serum levels reflect the blood burden. Normal serum nickel values in man are 0.2 - 0.3 μg/dl. Albumin is the main macromolecular carrier of nickel in a number of species, including man, while in man and rabbit there also appear to be nickel-specific proteins.

Tissue distribution of absorbed nickel appears to be dependent on the route of intake. Inhaled nickel carbonyl leads to highest levels in lung, brain, kidney, liver, and adrenals. Parenteral administration of nickel salts usually results in highest levels in the kidney, with significant uptake shown by endocrine glands, liver, and lung.

Based on animal studies, nickel appears to have a very short half-time in the body, several days, with little evidence for tissue accumulation.

The main excretory route of absorbed nickel in man and animals appears to be through the urine, with biliary excretion also occurring in experimental animals. While hair deposition of nickel also appears to be an excretory mechanism, the relative magnitude of this route, compared to urinary excretion, is not fully known at present.

A number of disease states or other physiological stresses can influence nickel metabolism in man. In particular, heart and renal disease, burn trauma, and heat exposure can either raise or lower serum nickel levels.

2.1.2 Subcellular and Cellular Aspects of Nickel Toxicity

Nickel, as the divalent ion, is known to bind to a variety of biomolecular species, such as nucleic acids and proteins, as well as their constituent units. Strongest interactions occur with sulfhydral, aza- and amino groups with binding to peptide (amido) and carboxylate ligands also possible.

A number of reports in the literature describe various *in vivo* and *in vitro* effects of various nickel compounds on enzyme systems as well as nucleic acid and protein biosynthesis. In particular, effects are seen on drug-detoxifying enzymes in various tissues, enzymes that mediate carbohydrate metabolism and enzymes that mediate transmembrane transport, such as ATPase.

A number of ultrastructural alterations are seen in cellular organelles from experimental animals exposed to various nickel compounds. Most of these changes involve the nucleus and mitochondria and range from slight changes in conformation to evidence of degeneration.

The behavior of cells in culture exposed to nickel compounds has been reported from different laboratories. Nickel ion, at varying levels, affects both viability and phagocytic activity of alveolar macrophages, which may explain the role of nickel in retarding resistance to respiratory tract infections.

Nickel-induced human lymphocyte transformation has been studied as a sensitive *in vitro* screening technique for nickel hypersensitivity and this procedure appears to be a reliable alternative to classical patch testing.

Various studies have been directed to the response of cells in culture to insoluble nickel dusts which are implicated in human and experimental animal carcinogenesis. In particular, rat embryo myoblasts show drastic reduction of mitotic index and viability when exposed to nickel subsulfide.

2.1.3 Systemic Toxicity of Nickel in Man and Animals

The toxicity of nickel to man and animals is a function of the chemical form of the element and the route of exposure.

For oral intake, nickel metal is relatively nontoxic, while nickel carbonate, nickel soaps, or nickel catalyst show effects only when dietary composition is at or exceeds 1000 ppm.

Exposure to nickel by inhalation, parenteral administration, or cutaneous contact is of considerably more significance to the picture of nickel toxicology.

In terms of human health effects, probably the most acutely toxic nickel compound is nickel carbonyl $Ni(CO)_4$. Exposure is usually through accidental release and inhalation by nickel workers. Acute nickel carbonyl poisoning is clinically manifested by both immediate and delayed symptomology. With the onset of the delayed, insidious symptomology there is constrictive chest pain, dry coughing, hyperpnea, cyanosis, occasional gastrointestinal symptoms, sweating, visual disturbances, and severe weakness. Most of these symptoms strongly resemble those of viral pneumonia.

The lung is the target organ in nickel carbonyl poisoning in both man and animals. The pathological pulmonary lesions observed in acute human exposure include pulmonary hemorrhage, edema and cellular derangement. Patients surviving an acute episode of exposure are frequently left with pulmonary fibroses.

From the literature, little is known about the effect of chronic nickel carbonyl exposure. In one reported case, such exposure was associated with asthma and Loffler's syndrome.

Adverse pulmonary effects for other nickel forms in occupational settings have been reported. Chronic rhinitis and sinusitis have been observed in workers engaged in nickel electroplating operations where the nickel species is nickel salt aerosol.

There is surprisingly little information in the literature about the effects of nickel on reproduction and development. Studies with both animals and humans indicate that nickel crosses the transplacental barrier and is taken up by the conceptus.

While gametotoxic effects of nickel have been demonstrated in animals, i.e., spermatogenesis impairment, there is no information on such exposures in man, particularly nickel workers.

There appear to be reproductive effects in animals after exposure to nickel given orally or parenterally, in the form of reduced litter size and decreased viability of newborn.

Teratogenic effects of nickel compounds have been noted in experimental animals, but have not been conclusively reported in man.

A number of effects of nickel on endocrine-mediated physiological processes have been observed. In carbohydrate metabolism, nickel induces a rapid transitory hyperglycemia in rats, rabbits, and domestic fowl after parenteral exposure to nickel (II) salts. These changes may be associated with effects on alpha and beta cells in the pancreatic islets of Langerhans. Nickel also appears to affect the hypothalamic tract in animals, decreasing the release of prolactin. Decreased iodine uptake by the thyroid has also been observed when nickel chloride is inhaled or ingested.

Nickel-induced nephropathy in man or animals has not been widely documented. Pathologic alterations of renal tubules and glomeruli have been seen in rats exposed to nickel carbonyl, while ingestion of nickel chloride by rats produces amino aciduria and proteinuria. Renal effects in man have mainly been clinically detected in acute exposures to nickel carbonyl.

Except for acute fatal exposures to nickel carbonyl, nickel compounds appear to possess low general neurotoxic potential. Lesions observed in neural tissue by nickel carbonyl include diffuse punctate hemorrhages, neural fiber degeneration, and marked edema.

Nickel subsulfide, when administered intrarenally to rats, provokes a pronounced, dose-dependent erythrocytosis associated with erythroid hyperplasia in bone marrow.

2.1.4 Nickel Carcinogenesis

A large number of experimental, clinical, and epidemiological studies have been carried out over the years directed to the role of nickel compounds in occupational and experimental carcinogenesis. Most of these studies have centered on a limited number of specific nickel compounds.

One can state generally that, of the compounds tested, most soluble nickel salts are noncarcinogenic while insoluble forms--such as metallic nickel, nickel subsulfide, and nickel oxide dusts--are variably carcinogenic. Among the insoluble compounds of nickel, the most carcinogenic form appears to be nickel subsulfide. However, there are exceptions to this generalization and it is possible that several mechanisms may exist for the manifestation of nickel carcinogenesis.

Various experimental models of nickel carcinogenesis have been described in the literature in the form of sarcomas, carcinomas, and mesotheliomas. In most of these animal models, sarcomas are elicited at the injection site of insoluble nickel dust, while injected nickel acetate induces lung adenocarcinomas and injected nickel carbonyl produces liver and kidney sarcomas.

Experimental data exist that demonstrate that nickel has a synergistic effect on the carcinogenicities of polycyclic aromatic hydrocarbons in laboratory animals and that it synergizes the activity of at least one virus, i.e. Newcastle Disease Virus.

Statistically excessive respiratory tract cancers in workmen at nickel refineries have been widely and conclusively documented. There is wide agreement that these are principally the effect of inhalation of respirable particles of metallic nickel, nickel subsulfide, nickel oxide, and nickel carbonyl. According to the International Agency for Research in Cancer: "Epidemiological studies conclusively demonstrate an excessive risk of cancer of the nasal cavity and lung in workers at nickel refineries. It is likely that nickel in some form(s) is carcinogenic to man."

Since respiratory tract cancers have occurred in industrial facilities that are diverse metallurgically in their operations, human carcinogenicity probably resides in several compounds of nickel. This would certainly be consistent with experimental models.

Other excess cancer risk categories involving nickel workers include laryngeal, gastric, soft tissue, and renal carcinomas, but these types are not as consistently seen as are the respiratory cancers.

As noted, nickel in the workplace has caused nasal cavity cancers, but the greater proportion of relatively smaller-sized particles in the general ambient environment compared to the workplace would likely lead to a greater particle deposition in the lungs versus the nasal cavities. Thus, while estimates of nasal cancer have been calculated, they have been presented primarily for comparative purposes. An estimate of the relative carcinogenic potency of nickel to other compounds has been calculated solely on lung and larynx cancer.

Two unit risk estimates are made for the lung cancer risk associated with lifetime exposure to 1 $\mu g/m^3$ of nickel in the ambient air. The validity of these estimates depends on several factors -- the accuracy of exposure estimates in the workplace, the similarity of nickel compounds in the workplace with those in the ambient air, the similarity of the physical forms of nickel in the two environments, and the validity of the extrapolation models used. All of these are very significant factors affecting the accuracy of a quantitative risk estimate or a range of estimates as has been attempted. The fact that most daily nickel exposure is not via inhalation but by the oral route suggests that some special, yet unknown, mechanism exists associating the physical form of the nickel with cancer of the respiratory tract.

Given these caveats, two unit risk extrapolations are made for nickel exposure in the ambient air. One is an animal-to-man extrapolation and the other is based on human occupational studies. Based on human occupational studies the estimates of respiratory cancer associated with a lifetime exposure to 1 $\mu g/m^3$ of nickel ranges from 7.5×10^{-5} to 5.8×10^{-4}. The upper limit unit risk estimate based on animal-to-man extrapolation is 4.8×10^{-3} for a lifetime exposure to 1 $\mu g/m^3$ of nickel sulfide.

The relative potency index for nickel compounds based on lung cancer in occupational studies by Pedersen and by Doll is $7\times10^{+1}$. This ranks in about the middle of the third quartile among the 53 substances which the EPA's Carcinogen Assessment Group has evaluated as suspect carcinogens.

No quantitative assessment has been attempted for nickel compounds taken orally because there is no direct evidence that nickel compounds are carcinogenic when ingested. On the other hand, no significant nickel feeding studies have been done; yet, dietary nickel remains the largest source of nickel exposure. This area remains a very significant unknown.

2.1.5 Dermatological Aspects of Nickel

Nickel dermatitis and other dermatological effects of nickel have been extensively documented in both nickel worker populations and populations at large.

Although the frequency of nickel dermatitis has abated considerably among nickel workers with advances in control technology and industrial medicine, it may still be a problem in electroplating shops.

Nonoccupational exposure to nickel leading to dermatitis includes nickel-containing jewelry, coins, tools, cooking utensils, stainless-steel kitchens, prostheses, and clothing fasteners.

Clinically, nickel dermatitis is usually manifested as a papular or papulovesicular dermatitis with a tendency toward lichenification, having the characteristics of atopic rather than eczematous dermatitis.

Conflicting data in the literature have muddied any clear relationship between atopic dermatitis and that elicited by nickel.

The hand eczema associated with nickel allergy appears to be of the pompholyx type, i.e., a recurring itching eruption with deeply seated fresh vesicles and little erythema localized on the palms, volar aspects, and sides of fingers.

A role for oral nickel in dermatitic responses by sensitive subjects has recently been described. Nickel-limited diets in one clinical trial resulted in marked improvement of the hand eczema in half of the subjects while in a second study, nickel added to the diets of patients appeared to aggravate the allergic response. Further study of oral nickel-nickel sensitivity relationships appears to be called for.

Nickel-containing implanted prostheses may provoke flare-ups of nickel dermatitis in nickel-sensitive individuals. The extent to which this is a problem appears to depend on the relative ease with which nickel can be solubilized from the surface of the devices by action of extracellular fluid.

The underlying mechanisms of nickel sensitivity presumably include diffusion of nickel through the skin and subsequent binding of nickel ion.

Useful animal experimental models of nickel sensitivity are few and when conducted, have only been under very specialized conditions.

2.1.6 Nickel as an Essential Element

There is a growing body of literature which establishes an essential role for nickel, at least in experimental animals.

One key criteria for element essentiality--existence of specific nickel-deficiency syndromes--is reasonably satisfied for nickel. Various researchers have shown different systemic lesions in various animals deprived of dietary nickel. Nickel deprivation has an effect on body weight, reproductive capability, and viability of offspring and induces an anemia through reduced absorption of iron.

Jack bean urease (and possibly rumen microbial urease) has been shown to be a nickel-requiring enzyme.

Further information in support of nickel as an essential element in animals is the apparent existence of a homeostatic mechanism for regulating nickel metabolism and the existence of nickel proteins in man and rabbit.

2.2 EPIDEMIOLOGICAL ASPECTS OF NICKEL'S EFFECTS

Studies on the impact of nickel on human populations are limited both as to number and the quality of experimental design. Much of the information of an epidemiological nature has been gathered in occupational settings, and it appears that only more recent data are sufficiently complete in terms of air nickel levels or indices of internal exposure. A major problem has been the quality of analytical methodology in earlier reports and only recently have acceptable methods evolved for measurements of nickel.

Studies of nonoccupational groups with reference to nickel exposure have been especially sparse. Some reports involve other pollutants, and the experimental designs reflect stratification of groups on the basis of exposure to other agents.

2.2.1 Nickel in Blood

Normal blood nickel levels, as measured in plasma or serum, in unexposed populations in the United States and elsewhere appear to be 0.2 to 0.3 μg/dl.

Exposed populations, mainly occupational study groups, have blood nickel values that are considerably above the normal figure, up to 3- to 4-fold. In a study comparing a control U.S. population and a Canadian group living in the vicinity of a nickel-processing complex, the mean value for the latter was about twice that of the reference mean level.

Complicating the evaluation of the levels of blood nickel in exposure categories are questions about smoking status, the nature of the nickel compounds in various workplace settings and the relative health status of subjects.

It does appear that blood nickel levels reflect intensity of exposure, rising rapidly with increase in exposure and falling correspondingly when such exposure is reduced. Thus, blood nickel levels are mainly of value in assessing the intensity of relatively recent or ongoing exposure.

2.2.2 Nickel in Urine

Problems with the assessment of urinary nickel in human subject groups overlap those for human blood nickel values, with an added problem of the feasible utility of total urinary output or urinary concentration from spot sampling.

Most studies of nonexposed subjects indicate urinary excretion of 2 to 3 μg nickel/day.

As with blood nickel, one can say generally that occupational exposure to nickel results in highly variable increases in urinary nickel output. In particular, nickel refinery workers can show urinary values of several hundred micrograms per liter.

It should be pointed out that, while average urine or blood nickel values for an exposure group relfect a given external exposure level, there is considerable individual variation.

2.2.3 Nickel in Human Hair

Attempts to relate nickel exposure to nickel levels in hair in various human study groups is complicated by the inherent difficulty of employing hair as a biological matrix for element assessment. Different laboratories use different techniques for both sample cleaning and sample collection.

Several studies have reported the relationship of nickel levels in hair in terms of urban versus rural settings. The data are inconclusive in demonstrating that hair levels reflect the amount of environmental exposure.

Nickel determinations in hair have not usually been carried out with industrial populations. In one study where this was done, there is no question that the levels of nickel in hair were markedly elevated over that of a reference group.

There are very few data concerning nickel tissue levels and total body burden in the literature. One estimate is that the total nickel burden in man is about 10 μg.

One can generally state that in nonoccupational groups, tissue levels of nickel are very low, in many cases below the detection capability of the method being used. Lung, liver, and kidney do appear to be somewhat higher in nickel than other tissues. In most of these studies, smoking status was not taken into account nor was the existence of disease states which might alter the levels of nickel in tissues.

information on tissue nickel levels for occupational categories are also limited. In cases of fatal nickel carbonyl poisoning, highest levels are seen in the lung, with lesser amounts in the kidney, liver, and brain.

2.2.4 Nickel Exposure and Nickel Hypersensitivity

There are essentially no studies of general populations which relate nickel exposure to the prevalence of nickel-related skin disorders, such as contact dermatitis. Much of the existing information evolves from either clinical or occupational groups having clinically demonstrable nickel hypersensitivity.

In a 1972 survey of a clinical population representing mainly the United States, the North American Contact Dermatitis Group reported that the prevalence for positive nickel reactions was higher for females than males, and the overall reaction rate was 11.2 percent. On a relative scale with other allergens, nine other agents had higher positive reaction rates.

The above survey and other limited data suggest that nickel sensitivity in the general population is more prevalent among women.

2.2.5 Human Carcinogenicity of Nickel

Epidemiologic data on the carcinogenicity of nickel has been reported for occupationally exposed nickel refinery workers in a number of countries. These studies have been reviewed and critiqued in other documents and there appears to be no doubt that increased cancer risk for the respiratory tract and nasal cavities exists in various operation categories for nickel refinery workers exposed to nickel subsulfide and nickel oxide dust, vapors of nickel carbonyl, and aerosols of soluble nickel salts.

Retrospectively, the relative cancer risk of respiratory tract cancers for nickel refinery workers was greatest prior to early changes in process and exposure abatement technology. Nevertheless, even with improved conditions some increased risk has continued, at least into the recent past.

Few of the occupational carcinogenesis studies of nickel workers have controlled for other factors which may influence the degree of cancer risk. One recent study has demonstrated that cigarette smoking among workers at a Norwegian nickel operation probably enhances the overall respiratory cancer risk, suggesting a synergistic effect between nickel and the polycyclic hydrocarbons.

The cancer risk status in workers exposed to nickel in work sites other than nickel refineries is not established at this time. A recent study of workers in an aircraft engine factory failed to demonstrate an increased relative cancer risk for workers exposed to nickel compounds. In this case, the atmospheric nickel levels were below 1 $\mu g/m^3$.

With regard to the general population, there are no data that suggest whether low-level nickel exposure does or does not lead to increased cancer risk. Such increased relative risk could be seen for rare tumor sites such as nasal cancers, but for the common respiratory cancers would never be statistically significant at ambient levels. Parenthetically, the lack of nasal cavity cancer deaths in the cigarette smoking population (with relatively high nickel intake) indicates that different forms of nickel exist in nickel refineries and cigarette smoke.

2.3 HUMAN HEALTH RISK ASSESSMENT OF NICKEL

2.3.1 Exposure Aspects

In terms of routes of nickel exposure of relevance to the general U.S. population, dietary sources are the main factor for nickel intake in man, daily ingestion being on the order of 300 to 600 µg nickel.

Percutaneous absorption of nickel from external contact with a wide variety of nickel-containing commodities is of further significance for those individuals with hypersensitivity to nickel.

In nonsmokers, the amounts of ambient air nickel entering the respiratory tract are quite small, an average of 0.2-0.4 µg/day (assuming a daily ventilation rate of 20 m^3). By contrast, cigarette smoking can contribute the major fraction of inhaled nickel, with estimates that smoking two packs of cigarettes will result in the inhalation of 3 to 15 µg nickel daily, approximately 10 to 40 times normal ambient air exposure. The possible amount of nickel inhaled through exposure to passive smoke is presently unknown and needs further consideration.

Levels of nickel in drinking water are also very low. A national survey for 1969-70 that involved 969 water supplies in the United States yielded a mean content of 4.8 µg nickel/ℓ water.

Nickel levels in soil of relevance to this section in terms of impact on man's terrestrial food chain vary considerably. Of less importance than the nickel content are soil type, soil pH, and classes of plants grown on the soil. Soil contamination occurs by virtue of man's activities and increased nickel-soil values have been obtained near roadways and nickel-emitting industrial operations. A potential source of increase in soil-nickel burden has to do with increased land spreading of municipal sewage sludges on agricultural lands.

2.3.2 Health Effects Summary

A variety of *in vitro* and *in vivo* effects of nickel compounds have been documented in experimental animals.

Occupational exposure to various nickel compounds has been associated with respiratory cancer and noncarcinogenic effects.

With reference to the various nickel-related health effects on the general population of the United States, nickel hypersensitivity in the form of contact dermatitis and associated skin disorders is the health effect of broad concern in this document due to the wide exposure to numerous nickel-containing commodities.

Some forms of nickel hypersensitivity, such as severe dermatitis, must be taken as a significant adverse response in terms of limiting activity and livelihood and predisposing individuals to further complications such as skin infections.

Nickel hypersensitivity as an underlying condition appears to be irreversible, although the frequency of flare-ups of such hypersensitivity may be ameliorated by limiting any obvious external contact.

2.3.3 Dose-Effect and Dose-Response Relationships of Nickel in Man

Assessment of dose-effect and dose-response relationships for nickel in man can be framed in the form of several questions:

(1) How do external exposure levels of nickel relate to internal indices of exposure?

(2) How do these internal indices of exposure relate to the eliciting and grade severity of critical effect(s) in critical tissue(s)?

(3) Is the information in answer to questions (1) and (2) sufficient to permit either modeling or statistical refinement of the data, to estimate what fraction of a study population is apt to develop a particular health effect at a given level of external exposure?

In general, literature dealing with the magnitude of nickel's effects on man is meager. This is due, in part, to the perception of nickel as an agent of lower toxicological potential than elements such as lead, cadmium or mercury in terms of chronic general population exposure. Such a perception is abetted by the fact that much of the literature over the years dealing with human health effects has appeared in the area of occupational hygiene.

With regard to dose aspects, the general population of the United States receives its major external exposure to nickel via ingestion or skin contact. Nickel inhalation is a comparatively minor source, although the extent of respiratory intake can be markedly increased in the case of cigarette smokers.

Of the daily dietary intake of 300 to 600 μg nickel, one to ten percent is absorbed. Thus, 3 to 60 μg can enter the bloodstream from the gastrointestinal tract. At present, it is not possible to state that factors such as age or nutritional status affect the extent of absorption.

Urban residents would inhale less than 1 μg nickel daily, of which some small fraction would be absorbed. Cigarette smoking could increase this amount considerably, with estimates that smoking two packs of cigarettes leads to inhaling 3 to 15 μg nickel daily, possibly in a form which would be extensively absorbed into the bloodstream.

Average drinking water levels are about 5 μg/ℓ. A typical consumption of two liters daily would yield an additional 10 μg of nickel, of which 1 μg could be absorbed.

As summarized earlier, urinary and serum/plasma nickel levels both appear to be indicators of nickel exposure. Taken collectively, occupational and limited nonoccupational group studies indicate that both urine and nickel levels will rise in response to increased nickel exposure and fall with exposure decrease, reflecting the intensity of relatively recent or ongoing exposure.

Several factors complicate exposure-physiological level relationships. In low-to-moderate nickel exposures, apparent homeostatic mechanisms control internal nickel movement in experimental animals. This may also be the case in man. Furthermore, nickel levels in media such as serum and urine change with a number of disease states.

In various experimental animal studies, there generally are demonstrable gradients in severity of different effects as controllable exposure levels are increased.

The corresponding case for man, mainly involving occupational exposure, permits one to also state generally that the extent of risk for carcinogenic and noncarcinogenic effects in nickel workers is increased with both the level of workplace exposure, e.g., respirable nickel, as well as the nature of the nickel compounds.

For both occupational and nonoccupational population groups it is difficult, but possible, to calculate the probable frequency of a given adverse effect at a given external nickel exposure level, i.e., dose-response curves. In nickel worker studies, there exists incomplete data or uncertainties about the specific chemical composition of nickel compounds in certain work sites. For nonoccupational groups such as individuals with nickel hypersensitivity who have skin contact with nickel-containing objects, the exposure parameter is difficult both to define and to estimate quantitatively. Nevertheless, at least for inhalation exposures, ambient air risk estimates based upon occupational exposure to nickel can be derived.

2.3.4 Populations at Risk

Among various subgroups of the U.S. population who may be at special risk for adverse effects of nickel are those who have nickel hypersensitivity and suffer chronic flare-ups of skin disorders with frank exposure. Within this category would be individuals predisposed to sensitization to nickel by virtue of familial history. In terms of the extent of nickel exposure among hypersensitive individuals, women who are housewives seem to be at particular risk.

The extent to which nickel in inhaled cigarette smoke is a cofactor in the demonstrated association of smoking with various respiratory disorders is not defined at present. The possibility of nickel, alone, or in synergism with other compounds, producing these various respiratory disorders places cigarette smokers in a potential risk category.

Nickel crosses the placental barrier in animals and apparently in man; thus, exposing the conceptus to nickel. There is no information at present that nickel exposure *in utero* under conditions of nickel exposure encountered by pregnant women in the U.S. population leads to adverse effects.

2.3.5 Numbers of the U.S. Population at Risk

No data base exists by which to determine the prevalence of nickel hypersensitivity in the general U.S. population.

Cigarette smokers, who may be at potential risk for any nickel-related respiratory disorders, number 54 million according to the American Cancer Society's 1982 figures.

3. NICKEL BACKGROUND INFORMATION

3.1 CHEMICAL/PHYSICOCHEMICAL ASPECTS

Nickel is a silvery metal with an atomic weight of 58.71 (derived from a composite of five stable isotopes), a melting point of 1455°C and a boiling point of 2900°C. Nickel is found in nature (along with such elements as arsenic, antimony, and sulfur) as the ores millerite (sulfide) and garnierite (silicate), the latter being the most commercially important form. Nickel is liberated via conversion to the sub-sulfide, Ni_3S_2, air-roasted to give nickel oxide, NiO, followed by carbon reduction to the metal.

In the Mond or carbonyl process (Mond, 1890), impure nickel is reacted with carbon monoxide at 50°C and ordinary pressures, or nickel-copper matte is reacted under pressure to give the volatile and highly toxic nickel carbonyl, $Ni(CO)_4$, which is thermally decomposed at 200°C to yield the metal in high purity.

The metal itself has good electrical and thermal conductivity properties and is easily drawn, rolled, forged, and polished. Its inertness to chemical attack accounts for its commercial value in electroplating.

The chemically most significant form of nickel is the divalent ion, which occurs in a myriad of simple compounds and coordination complexes. Of the inorganic derivatives, the insoluble oxides and sulfides and the soluble salts used in electroplating and other solution processes account for much of the toxicology associated with nickel.

In the atmosphere, nickel appears as particulate matter of variable chemical composition with the oxide being a major form from high-temperature emission sources. Nickel carbonyl is quite labile to decomposition and is oxidatively decarbonylated in open air (National Academy of Sciences, 1975).

Particulate size is of importance in terms of atmospheric movement, fallout processes and deposition in the human respiratory tract. In one report (Natusch et al., 1974), it was noted that nickel enrichment occurs in the smaller particulate fraction (< 1 μm) from coal-fired power plants, smaller particles being not only the most difficult to control but penetrating deepest into the lung. A study directed to the particulate size distribution in dust fall in Seattle, Washington, and San Jose, California, revealed that the percent of total nickel as a function of size range was: $\leq$43 μm, 27.5 percent; $\leq$840 μm, 75 percent, and 840-2,000 μm, 25 percent (National Academy of Sciences, 1975). More recent data show that ambient nickel is about equally divided between fine and course cuts approximately 50 percent of the time. The other 50 percent of the time, about twice as much particulate matter containing nickel is found in the fine fractions. (Akland, 1981).

In biological systems, the divalent nickel ion readily complexes with binding groups on various types of biomolecular species-proteins, peptides, DNA, amino acids, ATP (through interaction with nitrogen), sulfur and oxy groups, and such binding plays a role in its pharmacokinetics and toxicity. These complexes may be six-or four-coordinate.

3.2 ENVIRONMENTAL CYCLING OF NICKEL

Consumption of nickel in the United States for 1979 totalled about 196,000 tons (Predicasts, 1980) of which 70,000 tons were used in stainless steel production, 41,000 tons were used in nickel alloys (other than steel), 29,000 tons were used in electroplating, 20,000 tons were used in alloy steel production, and 18,000 tons were used in superalloys.

Of this annual consumption figure, some fraction is dissipated into various compartments of the environment, although the actual values cannot be determined from available information. Municipal incineration of general refuse containing nickel in diverse forms and soluble nickel salts in effluents dispersed to waters and municipal treatment facilities are two of the routes of entry. Augmenting such input are atmospheric emissions from fossil-fueled power plants and residential heating units, the former being a source of input which may increase in the future due to increased use of coal to fuel power plants. In addition, it is presently unclear whether burning wood for home heating purposes significantly contributes to atmospheric nickel emissions. Further research on this topic would be valuable in light of the increased home use of wood burning as a supplement to residential heating units.

In wastewaters, industrial sources account for over 50 percent of the observed nickel while residential sources supply up to 25 percent (Snodgrass, 1980). Industrial hazardous wastes containing nickel include spent plating baths/sludges from electroplating operations, spent pickle liquors/sludges from steel finishing operations and nickel carbonyl and nickel cyanide wastes from smelting and refining operations, powder metallurgy and chemical plant operations. Over 80 percent of nickel in influents of many wastewater treatment plants is soluble and removals vary from 10 to 40 percent (Snodgrass, 1980). The removal mechanism appears to be some uptake by biological solids of the soluble forms and subsequent removal by sedimentation.

The atmosphere is a major conduit for nickel, as particulate matter; contributions to atmospheric loading come from both natural sources and anthropogenic activity, with input from both stationary and mobile sources.

Various dry and wet precipitation processes remove particulate matter as washout or fallout from the atmosphere with transfer to soils and waters.

Soil-borne nickel may enter waters by surface runoff or by percolation into ground water. Once nickel is in surface and groundwater systems, physical-chemical interactions (complexation, precipitation/dissolution, adsorption/desorption, and oxidation/reduction) occur that will determine its fate and that of other chemical constituents (Richter and Theis, 1980).

Nickel may also undergo uptake by plants. Movement of airborne nickel into rainfall, soils, and vegetation has been well documented in the case of smelter operations (Hutchinson and Whitby, 1977; Regaini, et al., 1977; Beavington, 1975; Burkitt et al., 1972; Little and Martin, 1972; Goodman and Roberts, 1971). In addition, several reports have implicated auto traffic as a second factor in air emission of nickel resulting in subsequent fallout and movement of nickel into soils and vegetation (Burton and John, 1977; Lagerwerff and Specht, 1970).

The above studies also indicate that there is a relationship of soil and vegetation nickel to distance from the source as well as to existing wind patterns, decreasing with increasing distance except for transects lying in the wind path where the extension of contaminate range is relatively greater. Furthermore, there is a vertical gradient in soil nickel content, the greatest levels being measured in the top 5 cm.

Lability of nickel in soil is a function of pH, soil type and chemical exchange capacity. It is quite possible that in a given pollution setting other pollutants may affect such mobility. Hutchinson and Whitby (1977) found that soil pH around a nickel smelting complex was lowered enough to permit extensive aqueous extraction of soil-borne nickel.

3.3 LEVELS OF NICKEL IN VARIOUS MEDIA

Although it is not possible to furnish figures on the total input of nickel into the general environment of the United States, the extent of population exposure can be determined from levels of the element in various media encountered by the United States population.

3.3.1 Levels of Nickel in Ambient Air

The most comprehensive assessment of ambient air levels of nickel in the U.S. is that of the National Air Surveillance Network (NASN). Tabulation of air nickel levels for the period 1964 through 1969 are contained in the NAS Nickel Report (Nickel. National Academy of Sciences, 1975). More recent figures are available for the period 1970-1976 (Environmental Protection Agency, 1979).

Table 3-1 tabulates the air nickel averages for urban stations for the period 1970-1976. Table 3-2 presents the corresponding values for all nonurban stations for the same period. Table 3-3 presents the cumulative frequency distribution of individual 24-hour ambient air nickel levels for the years 1977-1980. This table also shows measurements obtained by two different networks--the hereto mentioned NASN network and the Inhalable Particulate Network (IP), which was initiated in 1979.

It may be seen from these tables that prior to 1975 ambient levels of nickel were generally below the limit of detection in both urban and nonurban areas. After 1976, detectable concentrations of nickel in ambient air samples were found in more than 50 percent of the samples. The observation that more samples were above the detection limit may be due in part to changes in analytical procedures, since newer analytical instrumentation was introduced in 1977.

It may also be seen from Table 3-3 that differences exist between the two monitoring networks. The differences in the arithmetic means in 1979--21 ng/m^3 versus 9 ng/m^3--are difficult to explain, especially when this difference is not apparent in 1980; nevertheless, it is still possible to generalize that the observed ambient air nickel concentrations have declined over the past several years.

Nearly all of the measurements of nickel in atmospheric aerosols have been made using optical emission spectroscopy (OES) of Hi-vol filter extracts and X-ray fluorescence spectroscopy (XRF) of dichotomous sampler filters. No suitable states exist in the nuclei of nickel isotopes for

TABLE 3-1. URBAN CUMULATIVE FREQUENCY DISTRIBUTIONS OF QUARTERLY COMPOSIT AMBIENT AIR NICKEL LEVELS

Year	No. of Sites	No. of Samples	Percentile[a] 30	50	70	99	Arithmetic Mean	(SD)
1970	92	797	LD[b]	LD	.019	0.127	NC[c]	NC
1971	101	717	LD	LD	.018	0.126	NC	NC
1972	96	708	LD	LD	.013	0.100	NC	NC
1973	83	559	LD	LD	.013	0.133	NC	NC
1974	93	594	LD	LD	.012	0.057	NC	NC
1975	171	695	LD	0.012	.019	0.062	0.014	0.014
1976	165	670	LD	0.014	.022	0.079	0.017	0.017

[a] Values under given percentile indicate the percentage of stations below the given air level. Values in μg/m³.

[b] Below the lower limit of discrimination, approximately 0.001 μg/m³ (for years 1970-1974).

[c] Statistics not calculated if more than 50 percent of the values are below the LD.

Source: Adapted from Environmental Protection Agency (1979). More recent data provided by Environmental Monitoring Systems Laboratory, Research Triangle Park, Environmental Protection Agency (Akland, 1981).

routine neutron activation analysis. The detection limits for both OES and XRF are of the order of 10 ng/m^3 for samples collected under normal conditions (typical sampler flow rates and 24 hour periods). In instances where nickel has been detected, it has been more often reported in urban aerosols. (Shaw and Stevens, 1980).

As previously stated, nickel is one of the metals associated with fossil-fuel combustion and residential heating units. This association is based on documented season-dependent gradients in air levels with highest levels in the winter quarter when space heating is at a maximum. Sulfur regulations which have been in effect over the period 1965-1974 appear to be the major factor in lower air nickel levels, particularly in the north-

TABLE 3-2. NONURBAN CUMULATIVE FREQUENCY DISTRIBUTIONS OF QUARTERLY COMPOSIT AMBIENT AIR NICKEL LEVELS OF QUARTERLY COMPOSITE SAMPLES

Year	No. of Sites	No. of Samples	Percentile[a] 30	50	70	99	Arithmetic Mean	(SD)
1970	7	124	LD[b]	LD	LD	0.076	NC[c]	NC
1971	3	94	LD	LD	LD	0.046	NC	NC
1972	10	137	LD	LD	LD	0.076	NC	NC
1973	11	100	LD	LD	LD	0.188	NC	NC
1974	5	79	LD	LD	LD	0.020	NC	NC
1975	20	98	LD	LD	LD	0.036	NC	NC
1976	15	98	LD	LD	LD	0.038	NC	NC

[a] Values under given percentile indicate the percentage of stations below the given air level. Values in μg/m³.

[b] Below the lower limit of discrimination, approximately 0.001 μg/m³.

[c] Statistics not calculated if more than 50 percent of the values are below the LD (for years 1970-74).

Source: Adapted from Environmental Protection Agency (1979). More recent data provided by Environmental Monitoring Systems Laboratory, Research Triangle Park, Environmental Protection Agency (Akland, 1981).

TABLE 3-3. CUMULATIVE FREQUENCY DISTRIBUTION OF INDIVIDUAL 24-HOUR AMBIENT AIR NICKEL LEVELS

Year	Network[a]	Sampler Type[b]	Number of Sites	Number of Observations	Percentile[c]				Arithmetic	
					30	50	70	99	Mean	(SD)
1977	NASN	HiVol	238	5400	0.006	0.006	0.009	0.062	0.012	(0.019)
1978	NASN	HiVol	195	4147	0.003	0.006	0.010	0.067	0.010	(0.022)
1979	NASN	HiVol	160	2931	0.003	0.005	0.010	0.057	0.009	(0.012)
	IP	HiVol	65	602	0.006	0.015	0.023	0.128	0.021	(0.022)
	IP	SSI	15	211	0.011	0.017	0.026	0.135	0.024	(0.023)
	IP	Dicot T	49	364	0.010	0.612	0.019	0.078	0.019	(0.018)
	IP	Dicot C	49	364	0.005	0.005	0.006	0.026	0.007	(0.006)
	IP	Dicot F	49	364	0.005	0.006	0.012	0.053	0.012	(0.012)
1980	NASN	HiVol	142	2881	0.002	0.003	0.007	0.052	0.007	(0.013)
	IP	HiVol	132	1731	0.002	0.004	0.009	0.062	0.009	(0.014)
	IP	SSI	105	1302	0.001	0.003	0.007	0.058	0.008	(0.013)
	IP	Dicot T	72	759	0.010	0.010	0.012	0.057	0.015	(0.012)
	IP	Dicot C	72	759	0.005	0.005	0.005	0.020	0.006	(0.003)
	IP	Dicot F	72	759	0.005	0.005	0.006	0.040	0.009	(0.010)

[a] Network: NASN is the National Air Surveillance Network which in 1980 was changed to the National Air Monitoring Filter Sites.
IP is the Inhalable Particulate Network.

[b] Sampler Type: HiVol is the high volume air sampler which collects particles less than 50 μm diameter.
SSI is the size selective (<15μm) version of the HiVol.
Dicot (T,C,F) is the dichotomous sampler where T is < 15μm, F is <2.5 μm, and C is the difference, i.e. greater than 2.5 μm and less than 15 μm.

[c] Values under given percentile indicate the percentage of stations below the given air level. Values in μg/m^3.

Source: Akland (1981).

eastern United States. Sulfur removal from residual oil necessitated by these regulations indirectly removes nickel as well (Faoro and McMullen, 1977). How long a trend to lower air nickel values in ambient air continues, in view of the above, will depend primarily on the future status of sulfur regulations as well as the level of fuel oil consumption.

3.3.2 Nickel in Drinking Water

Table 3-4 presents the values for nickel levels in 969 U. S. public water supplies for 1969-1970. The survey includes eight metropolitan areas (Nickel. National Academy of Sciences, 1975). The average value, taken at the consumer tap, was 4.8 μg/ℓ, with only 11 systems of this total exceeding 25 μg/ℓ. The highest level in one supply was 75 μg/ℓ.

Since the data in Table 3-4 do not furnish any measure of the number of people consuming drinking water of variable nickel content, the nickel levels for water supplies of the ten largest U.S. cities are listed in Table 3-5, based on the data of Durfor and Becker (1964).

The values for New York City, Chicago, and Los Angeles do not appear to be markedly at variance with the average concentration of 4.8 μg/ℓ nickel in water samples taken at the consumer's tap (Table 3-4).

TABLE 3-4. NICKEL LEVELS IN U.S. DRINKING WATER, 1969-1970[a]

Ni conc., mg/ℓ	No. of samples	Ni frequency (percent of samples)
0.000	543	21.69
0.001-0.005	1,082	43.22
0.006-0.010	640	25.57
0.011-0.015	167	6.68
0.016-0.020	46	1.84
0.021-0.025	14	0.56
0.026-0.030	4	0.16
0.031-0.035	2	0.08
0.036-0.040	1	0.04
0.041-0.045	1	0.04
0.046-0.050	1	0.04
0.051-0.055	1	0.04
0.075	1	0.04
Total	2,503	100.00

[a] Samples from 969 water systems.

Source: National Academy of Sciences (1975).

TABLE 3-5. NICKEL LEVELS OF DRINKING WATER OF 10 LARGEST U.S. CITIES

City	Nickel level, µg/ℓ
New York City	2.3[a]
Chicago	7.4[b]
Los Angeles	4.8
Philadelphia	13.0[a]
Detroit	5.6[a]
Houston	4.5[b]
Baltimore	4.7[b]
Dallas	5.2[b]
San Diego	<7.8
San Antonio	Not detected

[a] In storage.
[b] Post-treatment.

Source: Adapted from National Academy of Sciences (1975); values for 1962 survey of Durfor and Becker (1964).

3.3.3 Nickel in Food

The route by which most people in the general population receive the largest portion of daily nickel intake is through foods.

The assessment of average daily nickel intake in food can be done either by considering the aggregate nickel content of average diets in the population or by fecal nickel determinations. Although fecal nickel levels would be more meaningful than diet analysis, given the very small gastrointestinal absorption of nickel in man, such data have been sparse in the literature in terms of representative groups of individuals.

Some representative nickel values for various foodstuffs, adapted from data in the NAS Nickel Report (Nickel. National Academy of Sciences, 1975), are given in Table 3-6. These values have been obtained by different laboratories using different methods and may be dated in some cases.

Schroeder et al. (1962) calculated an average oral nickel intake by American adults of 300-600 µg/day, while Louria and co-workers (1972) arrived at a value of 500 µg/day. Murthy et al. (1973) calculated the daily food nickel intake in institutionalized children, 9-12 years old,

TABLE 3-6. NICKEL CONTENT OF VARIOUS CLASSES OF FOODS IN U.S. DIET

Food class and examples	Nickel content, ppm, wet weight
Grains/grain products	
Wheat flour, all-purpose	0.54
Bread, whole-wheat	1.33
Corn, fresh frozen	0.70
Rice, polished American	0.47
Rye flour	0.23
Rye bread	0.21
Fruits and vegetables	
Potatoes, raw	0.56
Peas, fresh frozen	0.30
Peas, canned	0.46
Beans, frozen	0.65
Beans, canned	0.17
Lettuce	0.14
Cabbage, white	0.32
Tomatoes, fresh	0.02
Tomato juice	0.05
Spinach, fresh	0.35
Celery, fresh	0.37
Apples	0.08
Bananas	0.34
Pears	0.20
Seafood	
Oysters, fresh	1.50
Clams, fresh	0.58
Shrimp	0.03
Scallops	0.04
Crabmeat, canned	0.03
Sardines, canned	0.21
Haddock, frozen	0.05
Swordfish, frozen	0.02
Salmon	1.70
Meats	
Pork (chops)	0.02
Lamb (chops)	Not detected
Beef (chuck)	Not detected
Beef (round)	Not detected

Source: Adapted from National Academy of Sciences (1975).

from 28 U.S. cities at an average value of 451 μg/day. In a related study, Myron et al. (1978) determined the nickel content of nine institutional diets in the U.S. and calculated an average intake of 165 μg/day.

Food processing methods apparently add to the nickel levels already present in foodstuffs via (1) leaching from nickel-containing alloys in food-processing equipment made from stainless steel, (2) the milling of flour, and (3) catalytic hydrogenation of fats and oils by use of nickel catalysts.

Several studies have reported daily fecal excretions of nickel. Nodiya (1972) reported a fecal excretion average of 258 μg in Russian students. Horak and Sunderman (1973) determined fecal excretions of nickel in 10 healthy subjects and arrived at a value of 258 μg/day, identical to the Russian study.

3.3.4 Nickel in Soil

Soil nickel levels are considered in this section chiefly from the aspect of the influence of soil nickel on man's food chain, e.g., plants → animals → man.

Soils normally contain nickel in a wide range of levels, 5-500 ppm, and soils from serpentine rock may contain as much as 5000 ppm (Nickel. National Academy of Sciences, 1975). While these levels may appear high in some instances, nickel content of soils, as such, is less important for plant uptake than such factors as soil composition, soil pH, organic matter in soil, and the classes of plants grown therein.

Natural levels of soil nickel may be added to by contamination from human activity such as atmospheric fallout in the areas of nickel-emitting industrial activities or auto traffic, as well as treatment of agricultural lands with nickel-containing superphosphate fertilizers or municipal sewage sludge.

In a study on the uptake of nickel by the edible portions of food crops such as bush beans, cabbage, onions, tomatoes, and potatoes grown in test pots in municipal sludge from Ithaca, N.Y., Furr et al. (1976) observed: (1) at first-year harvest, nickel levels in the above food crops were increased 2- to 3-fold compared to control soil crops, the corresponding soil pH levels being 7.1 for sludge-amended samples and 5.3 for control soils; (2) at second harvest, the increases seen in the first harvest did not recur, except for about a 2-fold increase in onions and tomatoes.

John and Van Laerhoven (1976) determined the effect of applying sludge at various loading rates on trace metal uptake by romaine lettuce and beets grown on amended soil with and without liming. Sludge used with unlimed soil significantly increased nickel levels in lettuce, did not affect the element level in beet tops, and reduced the nickel content of beet tubers. On the other hand, liming led to increases of nickel in all plant tissues at a 25 g/kg loading rate for one type of sludge (Milorganite) but not with a second type produced at a local treatment plant.

Frank et al. (1982) reported that aerial fallout from a nickel smelter at Port Colborne, Ontario, Canada, resulted in accumulation of nickel ranging from 600 to 6455 mg/kg in the organic soil of a farm. Vegetables have been grown commercially for 20 to 40 years on this farm located 1 km from the smelter and in direct line with the prevailing winds. In order to evaluate the possible impact of nickel contamination on the soil, nickel content of the edible parts of crops grown on this soil was determined. Nickel (mg/kg, dry weight) ranged from 80 to 280 in beet roots, 76 to 400 in cabbage heads, 15 to 395 in celery tops, 22 to 130 in lettuce tops and 24 to 140 in radish roots.

3.3.5 Nickel in Cigarettes

Cigarette smoking can contribute significantly to man's daily nickel intake by inhalation and nickel from this source probably exceeds the amount absorbed by breathing ambient air. An individual smoking two packs of cigarettes a day would inhale 1-5 mg of nickel per year or about 3-15 µg nickel daily (National Academy of Sciences, 1975). It is presently unknown what amount of nickel is inhaled by individuals subjected to passive smoke in indoor environments. Information on this topic is needed as such exposure may prove to be of importance for some individuals in certain working and home environments.

4. NICKEL METABOLISM IN MAN AND ANIMALS

4.1 ROUTES OF NICKEL ABSORPTION

The major routes of nickel absorption are inhalation and ingestion via the diet, with percutaneous absorption a less significant factor for nickel's systemic effects but important in the allergenic responses to nickel. Parenteral administration of nickel is mainly of interest to experimental studies and particularly helpful in assessing the kinetics of nickel transport, distribution, and excretion as well as maximizing the physiological parameters for nickel's effects. Transplacental transfer to the fetus is of importance in the assessment of *in utero* effects.

The relative magnitudes of nickel intake and absorption in humans are briefly summarized in the final portion of this section.

The amounts of nickel absorbed by organisms are determined not only by the quantities inhaled or ingested, but also by the chemical and physical forms of nickel. Other factors, such as host organism nutritional and physiological status, also play a role, but they have been little studied outside of investigations directed at an essential role for nickel.

4.1.1 Nickel Absorption by Inhalation

Respiratory absorption of various forms of nickel is probably the major route of nickel entry into man under conditions of occupational exposure, and considerable attention has been given to nickel inhaled as either the highly toxic nickel carbonyl or nickel particulate matter.

Nickel carbonyl, $Ni(CO)_4$, is a volatile, colorless liquid (b.p. 43°C). Armit (1908) found its relative toxicity to be 100-fold that of carbon monoxide. More recently, the threshold limit value (TLV) for a work day exposure has been set at 0.05 ppm (.35 mg/m^3), which may be compared to the corresponding value for hydrogen cyanide of 10 parts per million (ppm), or 200-fold greater (American Conference of Governmental Industrial Hygienists, 1981). Its presence and toxicological history as a workplace hazard followed closely upon the development of the Mond process of nickel purification in its processing (Mond et al., 1890). A detailed discussion of the toxicological aspects of nickel carbonyl poisoning is included in the NAS report on nickel (Nickel. National Academy of Sciences, 1975) as well as a recent review by Sunderman (1977).

Studies of nickel carbonyl metabolism by Sunderman and co-workers (Sunderman and Selin, 1968; Sunderman, Roszel, and Clark, 1968) indicate that pulmonary absorption is both rapid and extensive, the agent passing the alveolar wall intact. Sunderman and Selin (1968) observed that rats exposed to nickel carbonyl at 100 mg Ni/ℓ air for 15 minutes excreted 26 percent of the inhaled amount in the urine by 4 days post-exposure. On taking into account the exhaled quantity, as much as half of the inhaled amount could have been initially absorbed.

Few data exist on the pulmonary absorption of nickel from particulate matter deposited in the lung. The International Radiological Protection Commission (IRPC) Task Group on Lung Dynamics (1966) has advanced detailed deposition and clearance models for inhaled dusts of whatever chemical origin as a function of particle size, chemical properties, and compartmentalization within the pulmonary tract. Nickel oxide and nickel halides are classified as Class W compounds, i.e., compounds having moderate retention in the lungs and a clearance rate from the lungs of weeks in duration.

While the model described above has limitations, it can be of value in approximating deposition and clearance rates for nickel compounds of known particle size. For example, Natusch et al. (1974), based on a detailed study of eight coal-fired power plants, found that nickel is one of a number of elements emitted from these sources that is found in the smallest particles of escaped fly ash, approximately 1-2 μm mass median aerodynamic diameter (MMAD), this being a size that penetrates deepest into the pulmonary tract. According to the approaches of the IRPC model, particles of 1 μm undergo a total deposition percentage of 63 percent, with 30 percent in the nasopharyngeal tract, 8 percent in the tracheobronchial part, and 25 percent in the pulmonary compartment. The clearance rate of deposited particulate matter in the IRPC model is based on chemical homogeneity of the particulates, however, and one can only approximate such clearance if heterogeneous particles are considered. According to Natusch et al. (1974), nickel-enriched particles in fly ash have much of the nickel on the particle surface. If one approximates the clearance rate by assuming that particles enriched in nickel in the outer portions of the particle are handled by the model lung in a fashion similar to a homogeneous particle, then one obtains a total absorption (clearance) of approximately 6 percent, with major clearance, 5 percent, calculated as taking place from the pulmonary compartment.

Wehner and Craig (1972), in their studies of the effect of nickel oxide aerosols on the golden hamster, observed that inhalation by these animals of nickel oxide particles in a concentration of 2-160 μg/ℓ (2-160 mg/m^3) and particle size of 1.0-2.5 μm MMAD led to a deposition of 20 percent of the total amount inhaled. After 6 days post-exposure, 70 percent of the nickel oxide remained in the lungs, and even after 45 days approximately half the original deposition was still present. Since no material increase in nickel levels of other tissues had occurred, it appeared that absorption in this interval was negligible. In a later, related study (Wehner et al., 1975), co-inhalation of cigarette smoke showed no effect on either deposition or clearance.

Wehner et al. (1979) exposed Syrian hamsters to nickel-enriched fly ash aerosol (respirable concentration, approximately 185-200 μg fly ash/liter) for either 6 hours or 60 days and found that, in the short exposure, about 90 percent of 80 μg deposited in the deep tract remained 30 days after exposure, indicating very slow clearance. In the two-month study, the deep tract deposition was approximately 5.7 mg enriched fly ash, or 510 μg Ni. Thus, nickel leaching from the nickel-enriched fly ash in the hamster's lung does not occur to any extent and, while little systemic toxicity was seen in these animals over the experimental time frame, such forms of nickel in lung may be of importance in respiratory carcinogenesis.

In this connection, Hayes et al. (1978) found from scanning electron microscope studies that trace elements such as nickel are not uniformly distributed among particles of similar size; some particles carry much of the element for a given concentration determined by ordinary chemical analysis. Thus, in the Wehner et al. (1979) study, it is likely that the deep tract burden of relatively inert nickel contains some particles very high in nickel which would also suggest another risk factor for nickel respiratory carcinogenesis.

The implication of these two reports for human health risk are accentuated when considering the Natusch et al. (1974) report cited above that shows that respirable nickel-enriched fly ash is emitted from coal-fired power plants.

Leslie and co-workers (1976) have described their results from exposing rats to nickel and other elements contained in welding fumes. In this case, the particle size vs. nickel content was known precisely, highest nickel levels being determined in particles 0.5-1.0 μm in diameter at an air level of 8.4 μg Ni/m^3. While the authors did not determine the total nickel deposition in the lungs of these animals, they observed that essentially no clearance of the element from the lung had occurred within 24 hours, nor were there elevations in blood nickel, suggesting negligible absorption. In contrast, Graham et al. (1978), using mice and nickel chloride aerosol ($\leq$ 3 μm diameter, 110 mg Ni/m^3) found about 75 percent clearance by day 4 post-exposure. The rapid clearance of the nickel halide was probably due to its solubility relative to the oxide.

In addition to nickel exposure in man due to inhalation of ambient and workplace air, cigarette smoking constitutes a possible significant source among heavy smokers. Studies by Stahly (1973), Szadkowski and co-workers (1970), and Sunderman and Sunderman (1961a) indicate that 10-20 percent of cigarette nickel is carried in mainstream smoke, with better than 80 percent of this amount being in gaseous, rather than particulate, form. Since it is quite possible that nickel carbonyl constitutes the gaseous fraction (Sunderman and Sunderman, 1961a), one must assume that the relative absorption of nickel from cigarette smoke is proportionately greater than from airborne nickel particulates and with heavy smokers may be the main source of inhalatory nickel absorbed. Individuals smoking two packs of cigarettes daily can inhale up to 5 mg nickel annually (Nickel. National Academy of Sciences, 1975). By contrast, an individual in an urban U.S. area having an air level of Ni of 0.025 μg/m^3 (Nickel. National Academy of Sciences, 1975) and breathing 20 m^3 daily would inhale somewhat less than 0.2 mg. The relative significance for absorption would be even greater (vide supra). As stated previously, the effect of exposure to passive smoke remains an unknown in that nickel-specific studies addressing this problem have not been conducted.

4.1.2 Gastrointestinal Absorption of Nickel

Gastrointestinal intake of nickel by man is surprisingly high, relative to other toxic elements, which is at least partly accounted for by contributions of nickel from utensils and equipment in processing and home preparation of food.

Total daily dietary intake values may range up to 900 μg nickel, depending on the nature of the diet, with average values of 300-500 μg daily (Nickel. National Academy of Sciences, 1975).

Collectively, the data of Horak and Sunderman (1973), Nodiya (1972), Nomoto and Sunderman (1970), Perry and Perry (1959), and Tedeschi and Sunderman (1957) indicate that 1-10 percent of dietary nickel is absorbed.

One question that arises in considering the dietary intake and absorption of toxic elements has to do with the bioavailability of the agent in solid foodstuffs versus water and beverages. Ho and Furst (1973) observed that intubation of ^{63}Ni in dilute acid solution leads to 3-6 percent absorption of the radio-labeled nickel regardless of the dosing level. It does not appear, then, that nickel in simple aqueous solution is absorbed to any greater extent than that incorporated into the matrix of foodstuffs.

Fecal analysis more accurately reflects dietary intake where the rate of absorption is known and the existence and extent of biliary excretion is known. Diet profiles tend to be different than fecal analysis data owing to the obvious inherent difficulty of arriving at "true" diets for human subjects. In the case of nickel, where absorption is assumed to be small, the fecal analysis data approximate the low end of dietary profile estimates, and one can say that daily GI intake is probably 250-300 μg Ni/day.

4.1.3 Percutaneous Absorption of Nickel

Percutaneous absorption of nickel is mainly viewed as important in the dermatopathologic effects of this agent, such as contact dermatitis, and absorption viewed this way is restricted to the passage of nickel past the outermost layers of skin deep enough to bind with apoantigenic factors.

Wells (1956) demonstrated that divalent nickel penetrates the skin at sweat-duct and hair-follicle ostia and binds to keratin. Using cadaver skin, Kolpokov (1963) found that nickel (II) accumulated in the Malpighian layer, sweat glands and walls of blood vessels. Spruitt et al. (1965) have shown that nickel penetrates to the dermis.

Values for the amounts of nickel passing through outer layers of skin relative to amounts applied have not been determined. Samitz and Pomerantz (1958) have reported that the relative extent of nickel penetration is enhanced by sweat and detergents.

Mathur and co-workers (1977) have reported the systemic absorption of nickel from the skin using nickel sulfate at very high application rates.

After 30 days of exposure to nickel at doses of 60 and 100 mg Ni/kg, a number of testicular lesions were observed in rats, while hepatic effects were seen by 15 days at these exposure levels. It is not possible to calculate any absorption data from this study.

4.1.4 Transplacental Transfer of Nickel

Evidence for the transplacental transfer of nickel to the fetus dates to the study of Phatak and Patwardhan (1950) who found that newborn of rats fed nickel in various chemical forms had whole-body levels up to 22-30 ppm when mothers received 1000 ppm Ni in the diet.

Pregnant mice given nickel chloride intraperitoneally as one dose (3.5 mg/kg) at 16 days of gestation showed transfer to placental tissue with peak accumulation having occurred by eight hours post-exposure (Lu and co-workers, 1976).

Jacobsen et al. (1978), using ^{63}Ni-labeled nickel chloride and single intraperitoneal injections into pregnant mice at day 18 of gestation, showed rapid passage from mother to fetus, with fetal tissues generally showing higher concentrations than that of the mothers. Kidney levels were highest in the fetus with lowest levels being seen in brain. Furthermore, Olsen and Jonsen (1979) used ^{63}Ni whole body radiography in mice to determine that placental transfer occurs throughout gestation.

A similar study is that of Sunderman et al. (1978a), who administered ^{63}Ni-labeled solution to pregnant rats intramuscularly. Embryo and embryonic membrane showed measurable label by day eight of gestation, while autoradiograms demonstrated label in yolk sacs of placentae one day post-injection (day 18 of gestation).

Several reports indicate transplacental passage of nickel also occurs in man. Stack et al. (1976) showed levels of 11-19 ppm in dentition from four fetuses as well as a mean element concentration of 23 ppm in teeth from 25 cases of stillbirth and neonatal death.

Casey and Robinson (1978) found detectable levels of nickel in tissue samples from 40 fetuses of 22-43 weeks gestation, with levels in liver, heart and muscle being comparable to those seen in adult humans. Values ranged from 0.04-2.8 ppm (μg Ni/g dry weight). This study suggests ready movement of nickel into fetal tissues, given the similarity in fetal versus adult human levels.

Creason et al. (1976) studied the maternal-fetal tissue levels of 16 trace elements in eight selected U.S. communities. The authors reported geometric mean nickel levels of 3.8 μg/100 mℓ in maternal blood, 4.5 μg/100 mℓ in cord blood and 2.2 μg/100 g in placenta. In order to examine the relative levels of maternal and cord blood trace elements, ratios of these values were computed and a standard t-test was applied to the logs of these ratios. The geometric mean of the ratio for nickel was 1.15 based upon 166 observations. This ratio was not significantly different from 1 at the .05 level. While statistical significance was not shown, this study, nevertheless, indicated possible transplacental passage of nickel in humans.

4.2 TRANSPORT AND DEPOSITION OF NICKEL IN MAN AND EXPERIMENTAL ANIMALS

The kinetic processes governing the transport and distribution of nickel in various organisms are dependent upon the modes of absorption, the rate and level of nickel exposure, the chemical form of nickel and the physiological status of the organism.

Blood is the main vehicle for transport of absorbed nickel. While it is difficult to determine from the literature the exact partitioning of nickel between erythrocytes and plasma or serum for unexposed individuals, serum levels are rather good reflections of blood burden and exposure status (Nickel. National Academy of Sciences, 1975). In unexposed individuals, serum nickel values are approximately 0.2-0.3 μg/dl.

Distribution of serum-borne nickel among the various biomolecular components has been discussed in some detail in a recent review (Nickel. National Academy of Sciences, 1975), and it will mainly be noted here that serum albumin is the main carrier protein in sera of man, rabbit, rat, and bovine. Furthermore, there exists in sera of man and rabbits a nickel-rich metalloprotein identified as an α_1-macroglobulin (nickeloplasmin) in rabbits and in man as a 9.5 S α_1-glycoprotein. Sunderman (1977) has suggested that nickeloplasmin may be a complex of the α_1-glycoprotein with serum α_1-macroglobulin.

In vitro study of nickel (II) binding in human serum (Lucassen and Sarkar, 1979) shows histidine to be a major micromolecular binding species and an equilibrium between albumin and histidine may be the factor in blood to tissue transfer of nickel.

While the relative amounts of protein-bound nickel in sera of various species have a considerable range (Hendel and Sunderman, 1972) which reflect relative binding strengths of albumins, the total nickel levels are markedly similar, as may be seen in Table 4-1.

A number of studies of the distribution of nickel in experimental animals exposed to nickel carbonyl have been described (Nickel. National Academy of Sciences, 1975).

Armit (1908) exposed dogs, cats, and rabbits to nickel carbonyl vapor and was able to measure elevated nickel levels in lung, brain, kidney, and adrenal glands. Later investigators have observed elevated, rapidly cleared levels of nickel in lungs, brain, kidney, and liver of various animal species (Mikheyev, 1971; Sunderman and Selin, 1968; Ghiringhelli and Agamennone, 1957; Sunderman et al., 1957; Barnes and Denz, 1951).

Sunderman and Selin (1968) have shown that one day after exposure to inhaled ^{63}Ni-labeled nickel carbonyl, viscera contained about half of the total absorbed label with one-third in muscle and fat. Bone and connective tissue accounted for about one-sixth of the total. Spleen and pancreas also appear to take up an appreciable amount of nickel. Presumably, nickel

TABLE 4-1. SERUM NICKEL IN HEALTHY ADULTS OF SEVERAL SPECIES

Species (N)	Nickel concentration, μg/ℓ[a]
Domestic horse (4)	2.0 (1.3-2.5)
Man (47)	2.6 (1.1-4.6)
Jersey cattle (4)	2.6 (1.7-4.4)
Beagle dog (4)	2.7 (1.8-4.2)
Fischer rat (11)	2.7 (0.9-4.1)
British goat (3)	3.5 (2.7-4.4)
New Hampshire chicken (4)	3.6 (3.3-3.8)
Domestic cat (3)	3.7 (1.5-6.4)
Guinea pig (3)	4.1 (2.4-7.1)
Syrian hamster (3)	5.0 (4.2-5.6)
Yorkshire pig (7)	5.3 (3.5-8.3)
New Zealand rabbit (24)	9.3 (6.5-14.0)
Maine lobster (4)	12.4 (8.3-20.1)

[a] Mean (and range)

Source: Sunderman et al. (1972a).

carbonyl crosses the alveolar membrane intact from either route, inhalation or injection, suggesting that its stability is greater than has usually been assumed (Kasprzak and Sunderman, 1969; Sunderman et al., 1968; Sunderman and Selin, 1968). Retained nickel carbonyl undergoes decomposition to carbon monoxide and zero-valent nickel in the erythrocyte and tissues, followed by intracellular oxidation of the element to the divalent form and subsequent release into serum.

In human subjects acutely exposed to nickel carbonyl vapor, highest nickel levels were found in the lung, followed by kidney, liver, and brain (Nickel. National Academy of Sciences, 1975).

A number of reports in the literature describe the tissue distribution of divalent nickel following parenteral administration of nickel salts. These studies have been of two types: tissue nickel content assessment or studies measuring the kinetics of nickel deposition and clearance within a modeling framework. These data are summarized in Table 4-2.

It can be generally stated that nickel administered this way leads to highest accumulation in kidney, endocrine glands, lung, and liver. Relatively little nickel is lodged in neural tissue, consistent with the observed low neurotoxic potential of divalent nickel salts. Similarly, there is relatively slight uptake into bone, consistent with other evidence that nickel is rather rapidly and extensively cleared from organisms, with little retention in soft or mineral tissue.

Onkelinx et al. (1973) studied the kinetics of injected ^{63}Ni metabolism in rats and rabbits. In both species, a two-compartment model of clearance could be discerned, consisting of fast and slow components. In the rabbit, better than 75 percent of the dose was excreted within 24 hours, while comparable clearance in the rat required 3 days. In a later study, Onkelinx (1977) reported whole body kinetics of ^{63}Ni in rats. The time course of plasma nickel levels entailed first-order kinetics analyzable in terms of a two-compartment model. The major portion of nickel clearance is accounted for by renal excretion.

Chausmer (1976) has measured exchangeable nickel in the rat using ^{63}Ni given intravenously. Tissue exchangeable pools were directly estimated and compartmental analysis performed by computer evaluation of the relative isotope retention versus time. Kidney had the largest labile pool within 16 hours with two intracellular compartments. Liver, lung, and spleen

TABLE 4-2. TISSUE DISTRIBUTION OF NICKEL (II) AFTER PARENTERAL ADMINISTRATION

Species	N	Dosage	Relative distribution of ^{63}Ni	Reference
Mouse	8	6.2 mg/kg (one intraperitoneal injection)	Kidney > lung > plasma > liver > erythrocyte spleen > bladder > heart > brain > carcass (muscle, bone, and fat)	Wase et al. (1954)
Rat	4	617 µg/kg (one intravenous injection)	Kidney > lung > adrenal > ovary > heart > gastrointestinal tract > skin > eye > pancreas > spleen = liver > muscle > teeth > bone > brain = fat	Smith and Hackley (1968)
Guinea pig	6	1 mg/kg (subcutaneously for 5 days)	Kidney > pituitary > lung > liver > spleen > heart > adrenal > testis > pancreas > medulla oblongata = cerebrum = cerebellum	Clary (1975)
Rabbit	3	240 µg/kg (one intravenous injection)	Kidney > pituitary > serum > whole blood > skin > lung > heart > testis > pancreas > adrenal > duodenum > bone > spleen > liver > muscle > spinal cord > cerebellum > medulla oblongata = hypothalamus	Parker and Sunderman (1974)
Rabbit	4	4.5 µg/kg (intravenously for 34-38 days)	Kidney > pituitary > spleen > lung > skin > testis > serum = pancreas = adrenal > sclerae > duodenum = liver > whole blood > heart > bone > iris > muscle > cornea = cerebellum = hypothalamus > medulla oblongata > spinal cord > retina > lens > vitreous humor	Parker and Sunderman (1974)
Mouse	12	38.3 µg - or 76.6 µg/kg (10-20 µCi ^{63}Ni given intravenously in one dose)	Kidney > lung > sternal cartilage > pancreas	Oskarsson and Tjalve (1979)

Source: Adapted from National Academy of Sciences (1975).

pools could also be characterized by two compartments, while bone fit a one-compartment model. Corresponding half-times for the fast and slow components were several hours and several days, respectively.

Oral exposure of experimental animals to nickel with regard to absorption and tissue distribution appears to be dependent upon the relative amounts of the agent employed. Schroeder et al. (1974) could find no uptake of nickel in rats chronically exposed to nickel in drinking water (5 ppm) over the lifetime of the animals. Phatak and Patwardhan (1950) reported the effects of different nickel compounds given orally to rats in terms of tissue accumulation. Among the three chemical forms of nickel used, i.e., carbonate, nickel soaps, and metallic nickel catalyst, tissue levels were greatest in the groups fed the carbonate. O'Dell and co-workers (1971) fed calves supplemental nickel in the diet at levels of 62.5, 250, and 1000 ppm. While levels of nickel were somewhat elevated in pancreas, testis, and bone at 250 ppm, pronounced increases in these tissues were seen at 1000 ppm. Whanger (1973) exposed weanling rats to nickel (acetate) in the diet at levels up to 1000 ppm. As nickel exposure was increased, nickel content of kidney, liver, heart, and testis was also elevated, with greatest accumulation in the kidneys. Spears et al. (1978) observed that lambs given tracer levels of ^{63}Ni orally with or without supplemental nickel in diet had the highest levels of the label in kidney; the relative levels in kidney, lung and liver being less for the low-nickel group.

Comparison of the above studies suggests that a homeostatic mechanism exists to regulate low levels of nickel intake, e.g., 5 ppm, but such regulation is overwhelmed in the face of large levels of nickel challenge.

4.3 EXCRETION OF NICKEL IN MAN AND ANIMALS

The excretory routes for nickel in man and animals depend in part on the chemical forms of nickel and the mode of nickel intake.

Unabsorbed dietary nickel is simply lost in the feces. Given the relatively low extent of gastrointestinal absorption (vide supra), fecal levels of nickel roughly approximate daily dietary intake, 300-500 µg/day in man.

Urinary excretion in man and animals is usually the major clearance route for absorbed nickel. Reported normal levels in urine vary considerably in the literature, and earlier value variance probably reflects methodological limitations. More recent studies suggest values of 2-4 µg/ℓ (Andersen et al., 1978; McNeely et al., 1972).

While biliary excretion is known to occur in the rat (Smith and Hackley, 1968), the calf (O'Dell et al., 1971), and the rabbit (Onkelinx et al., 1973), what role it plays in nickel metabolism in man is unknown.

Sweat can constitute a major route of nickel excretion. Hohnadel and co-workers (1973) determined nickel levels in the sweat of healthy subjects sauna bathing for brief periods at 93°C to be 52 ± 36 μg/ℓ for men and 131 ± 65 μg/ℓ for women.

The role of nickel deposition in hair as an excretory mechanism in man has prompted a number of studies. The use of hair nickel levels in assessing overall nickel body burdens as well as exposure chronology remains to be widely accepted. Schroeder and Nason (1969) have reported sex-related differences in nickel levels of human hair samples, female subjects having nickel levels (3.96 μg/g, S.E.M. = ± 1.06) about fourfold those of men (0.97 μg/g, S.E.M. = ± 0.15). Such a difference, however, was not encountered by Nechay and Sunderman (1973) nor were their average sample values as high. The differences in these two studies serve to point out some of the difficulties in establishing quantitative relationships for the role of hair levels in nickel metabolism.

In experimental animals, urinary excretion is the main clearance route for nickel compounds introduced parenterally.

Animals exposed to nickel carbonyl via inhalation exhale a part of the respiratory burden of this agent within 2-4 hours, while the balance is slowly degraded *in vivo* to divalent nickel and carbon monoxide, with nickel eventually undergoing urinary excretion (Mikheyev, 1971; Sunderman and Selin, 1968).

The pattern of labeled-nickel urinary excretion in rats given a single injection (4 mg/kg, 12.5 μ Ci^{63}Ni/mg cold Ni, as chloride) was studied by Verma et al. (1980) who reported nickel to be excreted as a mixture of complexes within 24 hours of dosing, the ligating moieties having a molecular weight of 200-250.

4.4 FACTORS AFFECTING NICKEL METABOLISM

A number of disease states and other physiological stresses are reported to alter the movement and tissue distribution of nickel in man as well as experimental animals. Furthermore, *in vivo* movement of nickel may be deliberately altered to enhance nickel removal from the organism to minimize toxicity in cases of excessive exposure, specifically via the use of nickel chelating agents in the clinical management of nickel poisoning.

In man, increased levels of serum nickel are seen in cases of acute myocardial infarction (Sunderman et al., 1972a; McNeely et al., 1971; D'Alonzo and Pell, 1963), such alterations presently being considered as secondary to leukocytosis and leukocytolysis (Sunderman, 1977).

Serum nickel levels are also elevated in acute stroke and extensive burn injury (McNeely et al., 1971), while reduction is seen in hepatic cirrhosis or uremia, possibly secondary to hypoalbuminemia.

Palo and Savolainen (1973) report that hepatic nickel was increased tenfold over normal values in a deceased patient with aspartylglycosaminuria, a metabolic disorder characterized by reduced activity of aspartyl-β-glucosaminidase.

Other stresses appear to have an effect on nickel metabolism. Significant reduction in serum nickel has been seen in mill workers exposed to extremes of heat (Szadkowski et al., 1970), probably due to excessive nickel loss through sweating, as was noted earlier. While tissue nickel levels are reported to be elevated in rats during pregnancy (Spoerl and Kirchgessner, 1977), no comparable data are available for man.

The use of various classes of chelating agents to expedite the removal of nickel from man and animals has been reported with the goal of developing efficient chemotherapeutic agents for use in nickel poisoning. The data have been reviewed (Sunderman, 1977; Nickel. National Academy of Sciences, 1975) and will only be summarized in this section.

On the basis of reported clinical experience, sodium diethyldithiocarbamate (dithiocarb) is presently the drug of choice in the management of nickel carbonyl poisoning, being preferable overall to EDTA salts, 2, 3-dimercaptopropanol (BAL), and penicillamine. In all cases, the agents work to accelerate the urinary excretion of absorbed amounts of nickel before extensive tissue injury can result.

5. NICKEL TOXICOLOGY

Both acute and chronic effects of exposure to various nickel compounds have been extensively documented over the years, with those effects which are chronic in nature comprising both the bulk of available information and being most relevant to general population exposure.

5.1 ACUTE EFFECTS OF NICKEL EXPOSURE IN MAN AND ANIMALS

5.1.1 Human Studies

In terms of human health effects, probably the most acutely toxic nickel compound is nickel carbonyl, $Ni(CO)_4$, a volatile, colorless liquid formed when finely divided nickel comes into contact with carbon monoxide, as in the Mond process for purification of nickel (Mond et al., 1890). Its threshold limit value (TLV) for a work day is 0.05 parts per million (ppm) as compared to the corresponding value of 10 ppm for hydrogen cyanide (American Conference of Governmental Industrial Hygienists, 1981).

A sizable body of literature has developed over the years dealing with the acute inhalation exposure of nickel-processing workers to nickel carbonyl (Sunderman, 1977; National Institute for Occupational Safety and Health, 1977b; Nickel. National Academy of Sciences, 1975). Since much of this information is relevant mainly to industrial accidents and occupational medicine rather than general environmental health, it is not appropriate to accord it detailed discussion in this document.

According to Sunderman (1970) and Vuopala et al. (1970), who have studied the clinical course of acute nickel carbonyl poisoning in workmen, clinical manifestations include both immediate and delayed symptomatology. In the former, frontal headache, vertigo, nausea, vomiting, insomnia, and irritability are commonly seen, followed by an asymptomatic interval before the onset of insidious, more persistent symptoms. These include constrictive chest pains, dry coughing, hyperpnea, cyanosis, occasional gastrointestinal symptoms, sweating, visual disturbances, and severe weakness. Aside from the weakness and hyperpnea, the symptomatology strongly resembles that of viral pneumonia.

The lung is the target organ in nickel carbonyl poisoning in man and animals. Pathological pulmonary lesions observed in acute human exposure include pulmonary hemorrhage and edema accompanied by derangement of alveolar cells, degeneration of bronchial epithelium, and formation of fibrinous intra-alveolar exudate. Roentgenological follow-up on patients surviving acute episodes of exposure, frequently indicates pulmonary fibrosis.

In man, nephrotoxic effects of nickel have been clinically detected in some cases of accidental industrial exposure to nickel carbonyl (Carmichael, 1953; Brandes, 1934). This takes the form of renal edema with hyperemia and parenchymatous degeneration.

5.1.2 Animal Studies

The pronounced pulmonary tract lesion formation seen in animals acutely exposed to nickel carbonyl vapor strongly overlaps that reported for cases of acute industrial poisoning, and these have been tabulated in Table 5-1.

As in man, the lung is the target organ for effects of nickel carbonyl in animals regardless of the route of administration. The response of pulmonary tissue is very rapid, interstitial edema developing within 1 hour of exposure. There is subsequent proliferation and hyperplasia of bronchial epithelium and alveolar lining cells. By several days post-exposure, severe intra-alveolar edema with focal hemorrhage and pneumocyte cyel derangement has occurred. Death usually occurs by the fifth day. Animals surviving the acute responses show regression of cytological changes with fibroblastic proliferation within alveolar interstitium.

Acute renal injury with proteinuria and hyaline casts were observed by Azary (1879) in cats and dogs given nickel nitrate. Pathological lesions of renal tubules and glomeruli have been seen in rats exposed to nickel carbonyl (Hackett and Sunderman, 1967; Sunderman et al., 1961; Kincaid et al., 1953). Gitlitz et al. (1975) observed aminoaciduria and proteinuria in rats after single intraperitoneal injection of nickel chloride, the extent of the renal dysfunction being dose-dependent. Proteinuria was observed at a dose of 2 mg/kg, while higher dosing occasioned aminoaciduria. Ultrastructurally, the site of the effect within the kidney appears to be glomerular epithelium. These renal effects were seen to be transitory, abating by the fifth day.

5.2 CHRONIC EFFECTS OF NICKEL EXPOSURE IN MAN AND ANIMALS

5.2.1 Nickel Carcinogenesis

The present status of nickel's role in occupational and experimental carcinogenesis has been the subject of a number of recent reviews (Sunderman, 1981, 1979, 1977, 1976, 1973; National Institute for Occupational Safety

TABLE 5-1. ACUTE PULMONARY EFFECTS OF NICKEL CARBONYL EXPOSURE IN ANIMALS

Animal	Dosing	Effects	Reference
Rabbit	Inhalation 1.4 mg/l., 50 min	Intraalveolar hemorrhages, edema and exudate; alveolar cell degeneration by days 1-5	Armit, 1908
Rat	Inhalation 0.9 mg/l., 30 min	At 2-12 hr, capillary congestion and interstitial edema; at 1-3 hr days, intraalveolar edema; 4-10 days, pulmonary consolidation and interstitial fibrosis	Barnes and Denz, 1951
Rat	Inhalation 0.24 mg/l., 30 min	At 1 hr, pulmonary congestion and edema; at 12 hr-6 days, interstitial pneumonitis with focal atelectasis and peribronchial congestion	Kincaid et al., 1953
Rat, dog	Inhalation 1 mg/l., 30 min	At 1-2 days, intraalveolar edema and swelling of alveolar lining cells; at 3-5 days, inflamation, atelectasis and interstitial fibrolytic proliferation	Sunderman et al., 1961
Rat	I.V. 65 mg/kg, single dose	At 1-4 hr, perivascular edema; at 2-5 days, severe pneumonitis with intraalveolar edema, hemorrhage sub-pleural consolidation, hypertrophy and hyperplasia of alveolar lining cells	Hackett and Sunderman, 1967
Rat	I.V. 65 mg/kg, single dose	Ultrastructural alterations, including edema of endothelial cells at 6 hr and massive hypertrophy of membranes and granular pneumocytes at 2-6 days	Hackett and Sunderman, 1969

and Health, 1977a, 1977b; International Agency for Research on Cancer, 1976; National Academy of Sciences, 1975).

5.2.1.1 Experimental Animal Studies--The qualitative and quantitative character of the carcinogenic effects of nickel as seen in experimental animal models has been shown to vary with the chemical form of the nickel, the routes of exposure, the animal model employed (including strain differences within animal models), and the amounts of the substance employed.

Some of the experimental models of nickel carcinogenesis which have evolved out of various laboratories are given in Table 5-2, along with the various carcinogenic nickel compounds employed, the levels of material used, and the routes of administration. Responses are usually at the site of injection, although in the case of nickel acetate injection, pulmonary carcinomas were detected in mice given repeated intraperitoneal injections (Stoner et al., 1976). There have been no reports of experimental carcinogenesis induced by oral or cutaneous exposure.

Nickel metal, in the form of dust or pellets, leads to induction of malignant sarcomas at the site of dosing in rats, guinea pigs, and rabbits (Heath and Webb, 1967; Heath and Daniel, 1964; Mitchell et al., 1960; Hueper, 1955), while inhalation of nickel dust has been reported to lead to lung anaplastic carcinomas and adenocarcinomas (Hueper, 1958). In the inhalation study of nickel dust carcinogenesis, Hueper (1958) reported that an alveolar anaplastic carcinoma was found in one guinea pig lung, and a "metastic lesion" (lymph node) was found in a second animal. However, this study has been criticized as being inconclusive in that the lymph node tumor could not be associated with a primary lung tumor, nor were control animals used in the guinea pig experiment.

In a study of the carcinogenicities of various metal compounds, Gilman (1962) noted that nickel subsulfide (Ni_3S_2) was a potent inducer of rhabdomyosarcomas when given intramuscularly. Later studies of the carcinogenicity of nickel subsulfide demonstrated adenocarcinomas in rats given the substance intrarenally (Jasmin and Riopelle, 1976); rhabdomyosarcomas, fibrosarcomas, and fibrous histocytomas in rat testicular tissue after intratesticular dosing (Damjanov et al., 1978); and, epidermoid and adenocarcinomas in the lung in rats inhaling nickel subsulfide (Ottolenghi et al.,

TABLE 5-2. EXPERIMENTAL MODELS OF NICKEL CARCINOGENESIS

Animal	Agent	Dosing	Response	Reference
Rat, mice	Ni dust	Intrapleural/intraosseous: 0.06% suspension 5% suspension	Sarcomas	Hueper, 1955
Guinea pig	Ni dust	Inhalation 15 mg/m^3	Lung anaplastic carcinomas and adenocarcinomas	Hueper, 1958
Rat	Ni dust	I.M., 28 mg in serum	Rhabdomyosarcomas	Heath and Daniel, 1964; Heath and Webb, 1967
Rat	Ni dust	I.P., intrathoracic 5 mg in saline	Mesotheliomas	Furst et al., 1973
Rat	Ni pellet	S.C., 2 x 2 mm	Sarcomas	Mitchell et al., 1960
Rat, mouse	Ni_3S_2 or NiO dust	I.M., 20 mg/thigh	Rhabdomyosarcomas	Gilman, 1962
Syrian hamster	Ni_3S_2	I.M., 5 or 10 mg, single	Sarcomas	Sunderman et al., 1978b
Rat	Ni_3S_2	Inhalation 0.97 mg/m^3	Epidermoid carcinomas and adenocarcinomas (lung)	Ottolenghi et al., 1974
Rat	Ni_3S_2	Intrarenal 5 mg/saline or glycerol	Renal adenocarcinomas	Jasmin and Riopelle, 1976
Rat	Ni_3S_2	Intratesticular, 0.6-10 mg	Fibrosarcomas and rhabdomyosarcomas	Damjanov et al., 1978

TABLE 5-2 (continued)

Animal	Agent	Dosing	Response	Reference
Rat	$Ni(CO)_4$	Inhalation, 4-80 ppm	Epidermoid and anaplastic carcinoma, and adenocarcinomas (lung)	Sunderman et al., 1959; Sunderman and Donnelly, 1965
Rat	$Ni(CO)_4$	I.V., 50 µl/kg	Carcinomas and sarcomas	Lau et al., 1972
Mouse	$Ni(Oac)_2$	I.P., 360 mg/kg	Lung adenocarcinomas	Stoner et al., 1976
Rat, hamster	Nickelocene	I.M.	Sarcomas	Haro et al., 1968 Furst and Schlauder, 1971
Rat	Ni^3S^2/ Benzpyrene	I.M., 10 mg/5 mg	Sarcomas	Maenza et al., 1971
Rat	Ni^3S^2/ Benzpyrene	Intratracheal: 2-5 mg	Squamous cell carcinomas	Kasprzak et al., 1973
Rat	NiO/ methylcholanthrene	Intratracheal	Squamous cell carcinomas	Toda, 1962
Nude Mice	Hamster fetal cells transformed by Ni_3S_2 (0.1-1.0 µg/ml medium)	Subcutaneous injection	Sarcomas	Costa et al., 1979

TABLE 5-2 (continued)

Animal	Agent	Dosing	Response	Reference
Rat	Ni_3S_2 implanted in tracheas grafted under dorsal skin of isogenic recipients	1 or 3 mg Ni_3S_2/gelatin gelatin pellet implanted in tracheas 4 weeks post-grafting	10 percent carcinomas, 1 mg; 1.5 percent 3 mg; 67 percent fibro-/myosarcomas, 3 mg	Yarita and Nettesheim, 1978
Juvenile Rat	Ni_3S_2 injected into vitreous cavity of right eye	0.5 mg/rat	Malignant ocular tumors by 8 mos. in 14/15 treated rats	Sunderman et al., 1980a
Rat	Nickel (III) oxide,Ni_2O_3	3.0 mg of oxide/rat injected into cerebral cortex	By 21 mos, cerebral gliomas developed in 2 rats	Sosinski, 1975

1974). Hamster fetal cells transformed by Ni_3S_2 will induce sarcomas when injected subcutaneously into nude mice. In the study of Yarita and Nettesheim (1978) tracheas grafted onto isogenic rats showed mainly sarcomas but also a low yield of carcinomas with Ni_3S_2 implantation by as early as 6 months. Sunderman et al. (1980a) have extended the site tumorigenicity of Ni_3S_2 to the eye, where injection of 0.5 mg into the vitreous cavity in rats led to a high incidence of ocular tumors by 8 months.

Exposure to nickel carbonyl either via inhalation (Sunderman and Donnelly, 1965; Sunderman et al., 1959) or intravenously (Lau et al., 1972) has been observed to induce pulmonary carcinomas or carcinomas and sarcomas in organs such as liver and kidney, respectively. As noted above, repeated dosing intraperitoneally yields lung carcinomas in mice when nickel acetate is used (Stoner et al., 1976), while nickelocene, an organonickel "sandwich" structure, induces sarcomas in rats and hamsters when given intramuscularly (Furst and Schlauder, 1971; Haro et al., 1968).

Comparative carcinogenicity for various nickel compounds has been studied and demonstrated in various laboratories (Sunderman and Maenza, 1976; Jasmin and Riopelle, 1976; Payne, 1964; Gilman, 1962).

Sunderman and Maenza (1976) studied the incidence of sarcomas in Fischer rats within two years after single intramuscular injections of four insoluble nickel-containing powders: metallic nickel, nickel sulfide, α-nickel subsulfide and nickel-iron sulfide matte. Amorphous nickel sulfide had no tumorigenic potential, while nickel subsulfide was most active. The relative carcinogenicity of nickel-iron sulfide matte was intermediate between nickel subsulfide and metallic nickel powder, suggesting to these authors that there may also be a previously unrecognized carcinogenic potential in other nickel-sulfur mineral systems, as well as the corresponding arsenides, selenides, and tellurides.

In a later, related study, Sunderman et al. (1979b) studied the relative potential for carcinogenesis of alpha-Ni_3S_2, beta-NiS, Ni_3Se_2, Ni dust, the cyclopentadiene derivative of nickel carbonyl, amorphous NiS and NiSe. Using a single injection of 14 mg (as Ni) per animal and a 100 week interval, the percent incidence of site sarcomas were: alpha-Ni_3S_2 and beta-NiS, 100; Ni_3Se_2, 91; Ni dust, 65; NiSe, 50; cyclopentadiene-carbonyl complex, 19; and, amorphous NiS, 0 percent, respectively. Notable in this study was the marked effect of the crystalline form of NiS on reactivity;

amorphous sulfide had no tumorigenicity, while the beta-crystalline form was as potent as the subsulfide.

The above discussion has focused on nickel compounds used alone to induce carcinogenic responses. An equally important aspect of these effects is the synergizing action of nickel in the carcinogenicity of other agents, since environmental situations entail simultaneous exposure to a number of such substances.

Experimental data exist to demonstrate that nickel has a synergistic effect on the carcinogenicities of polycyclic aromatic hydrocarbons. Toda (1962) has found that 17 percent of rats receiving intratracheal doses of nickel oxide along with 20-methylcholanthrene developed squamous cell carcinomas; Maenza et al. (1971) demonstrated a synergistic, rather than additive, effect in the latency period reduction (30 percent) of sarcomas when simultaneous exposure to benzopyrene and nickel subsulfide was carried out. Kasprzak et al. (1973) observed pathological reactions in lungs of rats given both nickel subsulfide and benzopyrene that were greater than was the case for either agent alone.

Nickel and other elements are known to be present in asbestos and may possibly be a factor in asbestos carcinogenicity. The pertinent literature has been reviewed (Nickel. National Academy of Sciences, 1975; Morgan et al., 1973). Little in the way of experimental studies exists to shed light on any etiological role of nickel in asbestos carcinogenicity. Cralley (1971) has speculated that asbestos fibers may serve as a transport mechanism for metals into tissue and that the presence of chromium and manganese may enhance the carcinogenicity of nickel.

This possible synergizing effect between nickel and other elements or compounds also has implications in regard to the carcinogenicity of cigarettes, the nature and magnitude of this effect presently being unknown.

Virus-nickel synergism is suggested by the observation of Treagan and Furst (1970) that in vitro suppression of mouse L-cell interferon synthesis occurs in response to Newcastle Disease virus in the presence of nickel.

Looking at the literature in aggregate, there appears to be a general inverse relationship between solubility and carcinogenic potential in the nickel compounds that have been studied--insoluble nickel metal, nickel oxide, and nickel subsulfide generally being carcinogenic, while most nickel salts generally being non-carcinogenic. It has been suggested that the prolonged contact of the insoluble compounds is requisite to carcinogenic manifestation, the clearance of soluble nickel being shorter than the induction interval for such manifestation.

However, careful examination of the data reveals that the mechanisms leading to carcinogenic manifestation may be more complex than basic postulates regarding the solubility or insolubility of nickel compounds.

Examination of some of the inhalation studies suggests that particle size may interact significantly with solubility in determining the carcinogenic outcome. The smaller the particle, the deeper it goes in the respiratory tract (Task Group on Lung Dynamics, 1966) which provides a rationale for using small particles in studying carcinogenic responses in the lung itself. However, in retrospect, the smaller the nickel particle, the more efficiently it can be "neutralized" by the lung's defense mechanisms and removed by solubilization. To the extent that this shortens the contact time of the particle with tissue, it may minimize the likelihood of a carcinogenic response. This may have been the case in the negative report of Wehner et al. (1975) in which the investigators used nickel oxide, but at particle sizes of 0.3 μm mean diameter. Conversely, this was not the case for Ottolenghi et al. (1974) who used nickel subsulfide, also at small particle sizes (70 percent under 1.0 μm), but reported significant lung tumor incidence. The different results of these two studies further demonstrates the complexity of the issue.

In addition, in an experimentally well-designed study of Stoner et al. (1976), mice given repeated i.p. injections of nickel (II) acetate showed statistically significant incidence of pulmonary tumors at a level of 360 mg/kg, demonstrating that soluble compounds can be carcinogenic. It has been suggested that either movement of divalent nickel into the nucleus of cells in this particular animal model is greater or that cell division is more sensitive to nickel ion; thus, causing a carcinogenic response (Sunderman, 1981).

In regard to the mechanism for nickel carbonyl carcinogenicity, only a hypothesis can be presented at this time. It is known that nickel carbonyl passes the alveolar wall intact and subsequently is decarbonylated and oxidized from the zero-valent to the divalent state (Sunderman and Selen, 1968). Such oxidation requires a 2-electron transfer from nickel at the site(s) of oxidation and it may be that reactive intermediates, free radicals necessary in such transformation, have been responsible for provoking a neoplastic response roughly analogous to what happens in ionizing radiation.

From the above information, it therefore becomes apparent that there are likely several mechanisms for nickel carcinogenesis.

5.2.1.2 Clinical Studies--Statistically excessive respiratory tract cancers in workmen at nickel refineries have been widely and conclusively demonstrated, and there exists wide agreement that these are principally the effect of inhalation of respirable particles of metallic nickel, nickel subsulfide, nickel oxide, and nickel carbonyl (National Institute for Occupational Safety and Health, 1977a, 1977b; International Agency for Research on Cancer, 1976; Nickel. National Academy of Sciences, 1975). According to the International Agency for Research on Cancer (1976): "Epidemiological studies conclusively demonstrate an excessive risk of cancer of the nasal cavity and lung in workers at nickel refineries. It is likely that nickel in some form(s) is carcinogenic to man."

Inasmuch as respiratory tract cancers have occurred in industrial facilities that are metallurgically diverse in their operations, carcinogenicity probably resides in several compounds of nickel (Nickel. National Academy of Sciences, 1975). This is certainly consistent with the animal models of carcinogenicity described in the previous section. Furnace workers appear to have the highest risk in this regard, and freshly formed hot nickel dusts from some roasting procedures may be especially carcinogenic.

In Table 5-3 is an earlier tabulation (Nickel. National Academy of Sciences, 1975) of the numbers of different types of cancers of the lung and nasal cavities seen in nickel workers. As of March 1977, Sunderman (1977) had tabulated 477 cases of lung cancer and 143 cases of cancers of the nose and paranasal sinuses. Other excess cancer risk categories reported are laryngeal cancers in Norwegian nickel refinery workers (Pedersen et al., 1973), gastric and soft tissue carcinomas in Russian nickel refinery employees (Saknyn and Shabynina, 1973), and the relatively rare renal cancer in Canadian nickel electrolytic refinery workers (Sunderman, 1977).

5.2.1.3 Epidemiological Studies--Most of the epidemiological data on the carcinogenicity of nickel is contained in studies of occupationally exposed workers. Among these, nickel refinery workers have been studied most

TABLE 5-3. HISTOPATHOLOGICAL CLASSIFICATION OF CANCER OF THE LUNG AND NASAL CAVITIES IN NICKEL WORKERS

Tumor Classification	Lung Cancer		Nasal-Cavity Cancer	
	No.	%	No.	%
Epidermoid carcinoma (squamous cell)	34	69	22	45
Anaplastic (undifferentiated) carcinoma	13	27	6	12
Alveolar cell carcinoma	1	2	0	0
Adenocarcinoma	1	2	0	0
Columnar cell carcinoma	0	0	2	4
Spheroidal cell carcinoma	0	0	1	2
Spindle cell carcinoma	0	0	1	2
Scirrhus carcinoma	0	0	1	2
Pleomorphic carcinoma	0	0	15	31
Reticulum cell carcinoma	0	0	1	2
TOTALS	49	100	49	100

Source: National Academy of Sciences (1975).

extensively. Other occupations involving exposure to various nickel compounds have not been studied extensively and, consequently, the data available bears the limitations of initial exploration. The study populations at risk and the periods of exposure are fragmentary as are the potentials for the experience of mortality and development of detectable cancers in view of the latency periods of cancers. The following presentation will, therefore, be limited to data for nickel refinery workers.

The reports concern experience with cancer of the respiratory tract, specifically the lung and nasal cavities, among nickel refinery workers. The variety of processes for different raw nickel materials results in the production of different nickel compounds and, consequently, workers at specific refineries at different work stations are exposed in significantly different ways.

The data have been summarized and reviewed by numerous authors and, since the evidence is incontrovertible, there has been universal agreement that nickel refinery workers were, at least in the past, at significantly higher risk for cancer of the lungs and nasal cavity (Sunderman, 1977; National Institute for Occupational Safety and Health, 1977a, 1977b; International Agency for Research on Cancer, 1976; Nickel. National Academy of Sciences, 1975). Since these reviews, Lessard et al., (1978) have provided evidence that nickel refinery workers in New Caledonia also experience increased risk to lung cancers. Sunderman (1979), in a review, points out that in addition to the significantly higher risk for cancer of the lungs and nasal cavities, increased risk has been found for cancer of the larynx in Norwegian refinery workers and for gastric cancer and soft tissue sarcoma in Russian refinery workers.

The nickel compounds which are implicated are insoluble dusts of nickel subsulfide (Ni_3S_2) and nickel oxides (NiO and Ni_2O_3); the vapor of nickel carbonyl [$Ni(CO)_4$]; and soluble areosols of nickel sulfate, nitrate, or chloride ($NiSO_4$, $NiNO_3$, $NiCl_2$), (Sunderman, 1977).

The earliest epidemiological investigation of the increased risk of cancer is that of the nickel refinery workers at Clydach, Wales, where the Mond refining process had been used since the opening of the refinery in 1900. The mortality experience of these workers has been monitored continuously. The systematic retrospective investigations showed that there were significant changes in risk for workers beginning employment after 1925, the year when the refinery had undergone basic changes in the refinery processes which resulted in control of pollutants and decrease of exposure.

Doll et al. (1977) reported an update of the Clydach workers' studies. Due to the passage of time, the number of workers and the years at risk had increased, as had the period of observation of mortality. Table 5-4 shows the population and man-years for Clydach. Table 5-5 shows the findings for employment date cohorts and deaths from nasal sinus cancer, lung cancer, all other malignant neoplasms, and all other causes.

The effects of changes in production processes and pollution control likely contributed to the significant change of risk by 1930. In addition,

TABLE 5-4. NUMBER OF MEN FIRST EMPLOYED AT CLYDACH NICKEL REFINERY, WALES, AT DIFFERENT PERIODS AND MORTALITY OBSERVED AND EXPECTED FROM ALL CAUSES

Year of first employment	No. of men	Man-years of risk	Number of deaths Observed	Number of deaths Expected	Ratio of observed and expected deaths O/E
Before 1910	119	1,980.0	117	102.01	1.15
1910-14	150	2,666.5	137	92.84	1.48
1915-19	105	2,204.0	89	55.44	1.61
1920-24	285	7,126.5	209	146.25	1.43
1925-29	103	2,678.0	60	51.91	1.16
1930-44	205	4,538.5	77	60.42	1.27
All periods	967	21,193.5	689	508.87	1.35

Source: Doll et al. (1977).

it has been suggested that changes in the chemical composition of the raw material (Table 5-6) also affected the change in risk. The hypothesis that arsenic in the acid was responsible for the high lung cancer incidence in workers first exposed prior to 1925 has been put forth by some investigators. However, several lines of evidence, both from the study of other groups occupationally exposed to nickel compounds and experimental animals, indicate that this hypothesis is unlikely and that the nickel compounds themselves were the carcinogenic materials. For example, high cancer rates occured in Ontario nickel refineries where the sulfuric acid has always been arsenic-free (Sutherland, 1959). Also there is evidence that nickel sulfide and nickel oxide, both of which were present, are carcinogenic.

Whatever the exact reasons for the change in risk around 1930, the Clydach workers' studies establish the unquestionable existence of an increased risk for nasal and lung cancers in nickel refinery workers. The

TABLE 5-5. MORTALITY BY CAUSE AND YEAR OF FIRST EMPLOYMENT, CLYDACH NICKEL REFINERY, WALES

Year of first employment	No. deaths from nasal sinus cancer[a]			No. deaths from lung cancer			No. deaths from other malignant neoplasms			No. deaths from other diseases		
	Observed	Expected	Ratio O/E	Observed	Expected	O/E	Observed	Expected	Ratio O/E	Observed	Expected	Ratio O/E
Before 1910	14	0.036	389	24	2.389	10.0	10	14.637	0.68	69	84.95	0.81
1910-14	24	0.137	649	34	3.267	10.4	10	13.549	0.74	69	75.99	0.91
1915-19	11	0.025	440	20	3.070	6.5	10	8.064	1.24	48	44.28	1.08
1920-24	7 (1)	0.071	99	50	9.642	5.2	27	20.902	1.29	125	115.63	1.08
1925-29	0 (1)	0.026	0	9	3.615	2.5	7	7.247	0.97	44	41.02	1.07
All periods before 1930	56 (2)	0.195	287	137	21.983	6.2	64	64.399	0.99	355	361.87	0.98
1930-44	0	0.034	0	8	5.463	1.5	11	8.786	1.25	58	46.14	1.25

[a] Number of cases of nasal sinus cancer referred to as an associated cause of death shown in parentheses.

Source: Doll et al. (1977).

TABLE 5-6. CHRONOLOGICAL CHANGES IN THE FEED MATERIAL AT CLYDACH NICKEL REFINERY, WALES

	Composition of nickel matte							
Period	Ni, percent	Cu, percent	S, percent	Fe, percent	As, ppm	Se, ppm	Te, ppm	Pb, ppm
1902-33	40-45	35-40	16	1	0.3	trace	trace	trace
1933-64	75	2-6	23 reducing to 0.7	1	0.3	trace	trace	trace
1964-76	75	2-5	0.3	0.7	0.3-0.1	50	80	0.2-0.4

Source: Doll et al. (1977).

studies also represent the findings of a "natural experiment" in that they show significant decreases in these risks with significant removal of the pollutants.

Pedersen et al. (1973) studied Norwegian nickel refinery workers in a historical prospective study involving 1,916 men whose first employment at the Falconbridge refinery near Kristiansand had started prior to 1961 and who had been employed there for at least 3 years. Analysis was limited to those alive in 1953 and follow-up continued to 1971. The results were consistent with the results on Clydach workers first employed prior to 1930. These workers had a 3.75-fold increased risk of lung cancer as well as a 27-fold increased risk of nasal cavity cancer. However, in Norway the excess cancer deaths persisted at least up to the early 1950's. In addition, the excess risk from cancer of the larynx (International Classification of Disease-ICD 161) was also significant. Two updates of the study (Andersen et al. 1980; Pedersen and Andersen, 1978) had similar results. The 1978 update used 2,241 men followed through the end of 1976; this showed 62 lung cancers and 19 cancers of the nasal cavities. The 1980 update used 2,247 persons followed from 1953 to the end of 1979. In this latest update there were 21 cancers of the nasal cavities versus .88 expected for an observed to expected ratio of 23.9. For lung cancer the ratio was 3.7 (82 observed versus 22 expected). These ratios are only slightly smaller than those of the initial study.

Further analysis of the Norwegian lung cancer data was done by Kreyberg (1978), who was able to identify the histological character of the lung cancers, the cigarette smoking status, and the employment history of the lung cancer cases. The ability to control for these variables resulted in establishing that Group I cancers, epidermal and small cell anaplastic, were predominant and associated with cigarette smoking, Table 5-7. The latency period of these Group I cancers also explained the apparent anomalies in the development times for lung tumors when age at beginning of employment and age of beginning cigarette smoking had not been considered. Figure 5-1 shows the effect of the differences in age at first employment on the apparent decrease in latency period when defined as interval between beginning of employment and diagnosis.

The exposed workers still show an increased risk of lung cancer, though much of the risk appears to be attributable to cigarette smoking.

TABLE 5-7. SMOKING AND TUMOR INCIDENCE IN WORKERS AT THE FALCONBRIDGE NICKEL REFINERY

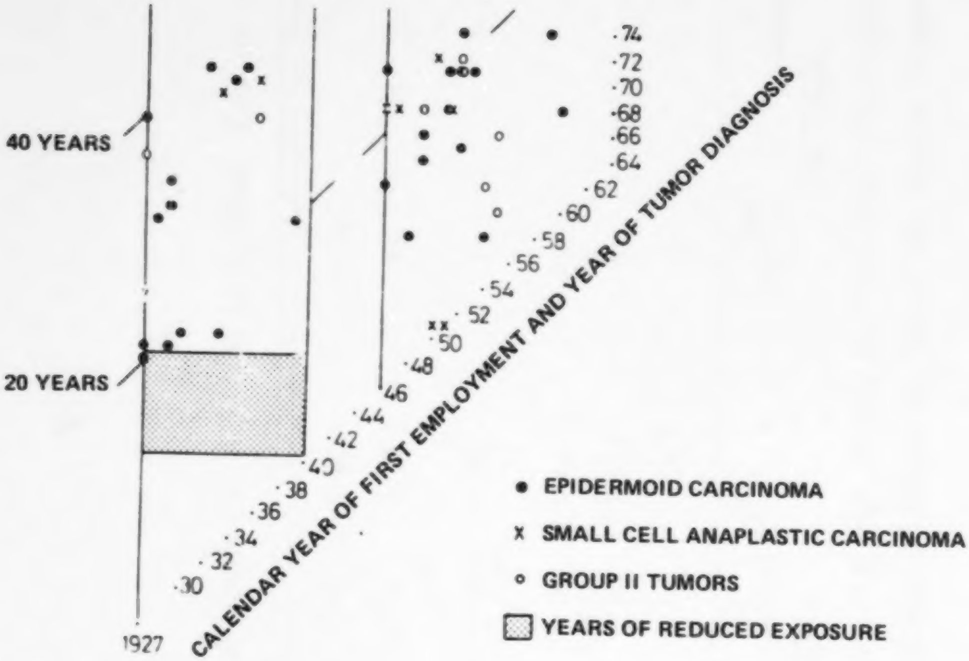
Type of tumor	Smokers	Nonsmokers
Series I		
Epidermoid carcinoma	10	3 (?)[a]
Small cell anaplastic carcinoma	2	0
Group II tumor	0	2
Series II		
Epidermoid carcinoma	13	0
Small cell anaplastic carcinoma	4	0
Adenocarcinoma	3	2

[a] Smoking history not ascertainable. Allocation as nonsmokers is the assumption against the hypothetical relationship.

Source: Kreyberg (1978).

Torjussen et al. (1979) reported on histopathological changes of the nasal mucosa in active and retired nickel workers from Falconbridge as well as controls. Biopsy materials were scored from 0 to 7, with 6 representing epithelial dysplasia and 7 carcinoma or carcinoma in situ. Table 5-8 reports the findings. There were two previously undetected cancers among the exposed active workers.

Quantitative analysis for nickel concentrations of nasal mucosa samples for the same individuals was also performed and reported by Torjussen and Andersen (1979). The nickel concentrations are shown in Table 5-9, and indicate that the nickel workers, whether active or retired, have much larger concentrations in these tissues than the controls. The elevated level in retired workers points to the body retention of nickel with moderate clearance.



Note: Reading up for 1939 and at dot reading to the right locates 1960: a case study who started work in 1939 and had diagnosis in 1960.

Figure 5-1. The scatter of occurrence of lung tumors related to time of first employment (abscissa) and time of diagnosis of tumor (ordinate).

Source: Kreyberg (1978).

TABLE 5-8. AVERAGE AND HIGH HISTOLOGICAL SCORES BY AGE GROUPS AND WORKING CATEGORIES

Category of subject/work	Average Score				High Score	
	Age groups (years) <45	46-59	>60	All	percent 6 score	percent 7 score
Roasting/smelting	2.83	3.22	3.86	3.25	12	2
Electrolysis	2.64	3.15	3.24	3.01	11	-
Non-process	1.95	2.50	3.00	2.49	10	-
Active nickel workers	2.55	3.01	3.36	2.96	12	0.6
Retired nickel workers	--	--	4.93	4.93	47	-
Controls	1.78	2.13	1.60	1.88	2*	-

*Carpenter, 65 years old (wood dust exposure is accepted as increased occupational risk for cancer of nasal sinus).

Source: Adapted from Torjussen et al. (1979).

TABLE 5-9. NICKEL CONCENTRATIONS IN NASAL MUCOSA IN NICKEL WORKERS, RETIRED NICKEL WORKERS AND CONTROLS

Category of subjects/work	Number of subjects	Concentration (μg/100 g, wet weight) Mean	SD±
Roasting/smelting	97	467.2	594.6
Electrolysis	144	178.1	234.7
Non-process	77	211.1	300.7
All nickel workers	318	273.9	412.1
Retired nickel workers	15	114.4	178.2
Controls	57	12.9	20.3

Source: Torjussen and Andersen (1979).

Correlation between nickel concentrations in the mucosa and years of retirement was examined and the correlation coefficient was reported as r = -0.434 (which was statistically significant in a one-sided test). Figure 5-2 shows these data.

The work from Falconbridge indicates that sophisticated screening and diagnostic procedures can and do locate unknown cancers and cancers *in situ* among nickel refinery workers and bring dysplasias under surveillance, so that mortality may be prevented or reduced. Nelems et al. (1979), in a study of Canadian nickel refinery workers, reported identification of 12 workers among 268 screened who had cancerous lesions or sputum changes. Mortality in 10 has been prevented at the time of reporting. The cancers had been unknown and were located in the respiratory tract, ranging from the maxillary sinus or larynx to the lung itself.

Another historical prospective study was conducted in 1959 by Sutherland among Canadian nickel refinery workers in Port Colborne, Ontario. Sutherland gathered data on all employees at the refinery with five years or more of service who were on the payroll in January 1930. Age specific male death rates from Ontario were used to calculate the expected number of deaths in

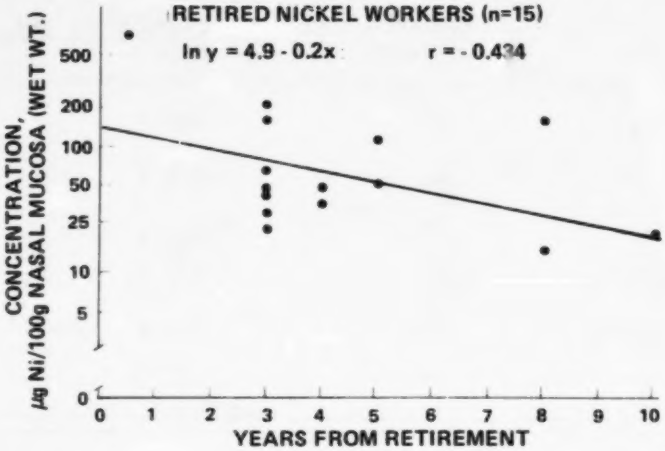


Figure 5-2. The correlation between the nickel concentrations in the mucosa of 15 retired workers and the number of years after retirement.

Source: Torjussen and Anderson (1979).

the refinery cohort. Sutherland found that these workers had 2.2 times the expected number of deaths from lung cancer and 37 times the expected deaths from nasal cavity cancer. An updating of this study to include deaths until 1974 shows similar relative risks (International Nickel Company, 1976). Environmental studies reported on the plant indicated high exposure to nickel dust (Sutherland, 1959) and nickel oxide (National Institute of Occupational Safety and Health, 1977a), as well as other nickel compounds. As mentioned above, this study provides evidence against the hypothesis that arsenic was the carcinogenic agent to which Clydach workers were exposed prior to 1925, since sulfuric acid used in Ontario refineries has always been arsenic-free.

Although epidemiological occupational studies provide substantial evidence that exposure to airborne nickel in dust, mist, or fumes increases the risk of respiratory cancer, it is difficult to determine which nickel compounds are carcinogenic in the occupational setting. In nickel refineries, exposure to several nickel compounds occurs simultaneously. Attention has been focused on the respirable particles of nickel, nickel sulfide, nickel oxide, and carbonyl vapor as the possible causes of cancer.

5.2.1.4 In-Vitro/In-Vivo Correlates of Nickel Carcinogenesis--A number of studies employing nickel compounds in various tests systems and *in vivo* data have been reported which shed light on some of the mechanisms by which carcinogenic metals in general, and nickel in particular, may express such effects in intact organisms. A recent review by Sunderman (1979) has summarized much of the pertinent literature. These test systems are tabulated in Table 5-10.

Several authors have noted that the nucleus is enriched in nickel when different nickel compounds are employed in various experimental systems to assess subcellular distribution of the element. Webb and coworkers (1972) found that 70-90 percent of nickel in nickel-induced rhabdomyosarcomas is sequestered in the nucleus, of which half is in the nucleolus and half in nuclear sap and chromatin. Furthermore, nickel binding to RNA/DNA has been shown by both Beach and Sunderman (1970), using $Ni(CO_4)$ and rat hepatocytes, and Heath and Webb (1967), in nuclei from Ni_3S_2-induced rat rhabdomyosarcomas. *In vivo* inhibition of RNA synthesis by nickel compounds has also been demonstrated (Witschi, 1972; Beach and Sunderman, 1970).

TABLE 5-10. IN-VITRO/IN-VIVO CORRELATES OF NICKEL CARCINOGENESIS

System	Ni Compound	Response	Reference
Intracellular distribution of nickel in rhabdomyosarcomas	Ni_3S_2	Nickel levels highest in nucleus, (70-90 percent) with half in nucleolus	Webb and coworkers, 1972
Intracellular distribution of nickel in hepatic cells	$Ni(CO)_4$	Nucleus is enriched in nickel, the element bound to an RNA polymerase-chromatin complex	Beach and Sunderman, 1970
In vivo effects on RNA synthesis in rat hepatocytes	$Ni(CO)_4$	Inhibition of RNA synthesis	Sunderman and Esfahani, 1968; Beach and Sunderman, 1969
In vitro effects on DNA synthesis in rat embryo cells	Ni_3S_2	Inhibition of DNA synthesis	Basrur and Gilman, 1967
DNA polymerase from *E. coli*	Ni(II)ion/ 5 mM Ni	Fidelity of DNA synthesis altered	Miyaki et al., 1977
DNA polymerase from avian myeloblastosis virus	Ni(II) ion/ 5 mM Ni	Fidelity of Mg-activated DNA synthesis altered	Sirover and Loeb, 1977
Morphological transformation potency for Syrian hamster embryo cells	Ni_3S_2, Ni_3Se_2, Ni dust	All three agents significantly enhanced transformation as indexed by frequency of cell colony piling up/test plate	Costa et al., 1978
Enhancement of transformation of hamster embryo cells by simian adenovirus, SA 7	Ni(11) ion/0.38 mM	Enhancement demonstrated by both relative increase in viral transformation frequency and absolute increase in number of transformed loci among treated cells	Casto et al., 1979a

TABLE 5-10. (continued)

System	Ni Compound	Response	Reference
Transplacental *in vivo*/*in vitro* morphological transformation of hamster embryo cells	Ni(II) ion/ injection into pregnant hamsters, 5mg/ 100g b.w.	Enhanced transformation observed in cells cloned from third sub-passage	DiPaolo and Casto, 1979
Transformation of Rauscher leukemia virus-infected rat embryo cells using attachment independence as end point	Ni(II) ion/conc. not stated	Greater than 100 percent increase in transformed cell survival relative to controls (neoplastic transformation results in attachment independence which is required for cell survival in the plate technique used)	Traul et al., 1979
Effect on increased integration of viral genome in simian adenovirus (SA-7) - transformed hamster embryo cells	Ni(II) ion/50-200 μg Ni/ml culture	Increased amounts of SA7 - DNA were incorporated into cellular DNA, 2-9 days past treatment, versus controls	Casto et al., 1979b

Several reports, those of Sirover and Loeb (1977) and Miyaki et al. (1977), document the effect of nickel ion (nickel sulfate) in increasing the error rate (decreasing the fidelity) of DNA polymerase in E. coli and avian myeloblastosis virus.

A number of studies (Table 5-10) using test systems of varying complexity have documented both the direct cellular neoplastic transformation potency of soluble nickel (nickel sulfate) and insoluble Ni_3S_2, Ni_3Se_2 and nickel dust, as well as the further enhancement of transformation due to viral inoculation (DiPaolo and Casto, 1979; Traul et al., 1979; Casto et al., 1979a, 1979b; Costa et al., 1978). In one study, (Casto et al., 1979b) the nickel (II) enhancement of transformation in virally-infected cells was seen to involve increased amounts of viral (SA7) DNA into cellular DNA, suggesting that enhancement of viral transformation results from damage to cell DNA, which then increases the loci for attachment of viral DNA.

In hamster cells in culture, nickel compounds have been shown to induce DNA strand breaks (Robison and Costa, 1982; Robison et al., 1982) and DNA repair synthetics (Robison et al., 1983). Recently, nickel has also been shown to form a protein-nickel-DNA complex in mammalian systems (Lee et al., 1982; Ciccarelli et al., 1981). These observations suggest that nickel compounds with carcinogenic activities can induce damage to DNA and form DNA-protein crosslinks.

5.2.2 Nickel Mutagenicity

5.2.2.1 Nickel Mutagenesis in Experimental Systems--The mutagenic activity of nickel compounds has been reviewed by Flessel (1979) and Sunderman (1981).

Some recent reports involving eukaryotic cell culture systems treated with various nickel compounds indicate some mutagenic potential (Wulf, 1980; Amacher and Paillet, 1980; Nishimura and Umeda, 1979; Umeda and Nishimura, 1979; Miyaki et al., 1979).

Miyaki et al. (1979) examined the mutations at the hypoxanthine-guanine phosphoribosyl transferase locus in Chinese hamster V79 cells induced by nickel chloride, using development of resistance to 8-azoguanine as the endpoint. "Weak" mutagenicity, in the words of the authors, was noted at nickel concentrations up to 0.8 millimolar but, as the authors pointed out, the cytotoxicity of the nickel ion was such as to preclude study of higher concentrations. It is possible that a dose-response relationship would exist at increasing levels, if cytotoxicity did not intervene. However, in the actual case, cell toxicity becomes the endpoint for concern, not mutagenicity, with elevated levels.

It should be noted that this cell culture study cannot be compared directly to the microbial assay systems, in part because of cell membrane permeability differences in mammalian versus microbial cells (vide infra).

Amacher and Paillet (1980) tested seven inorganic metal salts, including nickel chloride, for their potential to induce trifluorothymidine-resistant (TFT^{Res}) mutants in $L5178Y/TK^{+/-}$ mouse lymphoma cell by directly exposing cells to varied doses of each compound for three hours. Nickel chloride consistently produced dose-related increases in the absolute number of TFT^{Res} mutants as well as increases in mutation frequencies at compound concentrations permitting greater than 20 percent survival (cytotoxicity precluding the study of mutants at higher concentrations). Cell survival as percent of control ranged from 5 percent at 7.12×10^{-4} M to 49 percent at 2.25×10^{-4} M. Corresponding mutation frequencies (per 10^4 survivors) ranged from 1.52 to 0.33, respectively. Cultures treated with 1 percent saline for three hours served as controls. At 100 percent cell survival, controls had a mutation frequency of 0.20. The authors did not report any statistical analysis distinguishing controls from treated cultures.

Wulf (1980) investigated sister chromatid exchange (SCE) in human lymphocytes exposed to nickel ion as sulfate at levels of 2.33×10^{-3} to 2.33×10^{-6} mol/ℓ. In the SCE test system, the relative increase in SCE produced compared to controls is taken as a measure of mutagenic potential. At all concentrations, the number of SCE was significantly higher (one-sided Student's t-test) than in the control series, with the exception of the highest level where the cytotoxicity to the cells was too severe to assess SCE. Each time the nickel concentration was increased 10 times, the SCE count increased approximately 20 percent indicating a dose-response relationship: at 10^{-4} mol/ℓ the increase was 56 percent versus controls ($p < .0005$); at 10^{-5} the increase was 36 percent ($p < .0025$); and at 10^{-6} the increase was 16 percent ($p < .5$).

The induction of chromosomal aberrations in FM3A mammary carcinoma cells (from C3H mice) in culture, using nickel chloride, nickel acetate, potassium cyanonicklate ($K_2Ni(CN)_4$) and nickel sulfide, was studied by

Umeda and Nishimura (1979). Nickel chloride and nickel acetate induced few aberrations when tested at levels of 1.0×10^{-3}, 6.4×10^{-4}, 3.2×10^{-4} and 2.0×10^{-4} M for up to 48 hours. Potassium cyanonicklate, at the same levels, induced definite increases in aberrant metaphase cells which consisted mainly of gaps. The aberrant frequency for this compound at 48 hours was 37, 28, 8 and 12 percent for the above mentioned levels. Nickel sulfide also showed a definite increase in the frequency of aberrant metaphases at 48 hours--29 percent at 1.0×10^{-3}; 12 percent at 6.4×10^{-4}, and 2 percent at 3.2×10^{-4}. Although all four compounds demonstrated toxicity at a concentration of 10^{-3} M, their respective abilities to induce chromosomal aberrations were quite variable and no clear dose-response trends emerged for any of the compounds. In addition, the authors reported (Nishimura and Umeda, 1979) that the chromosomal aberration data for the $Ni(CN)_4^{-2}$ anion was possibly complicated by the mutagenic behavior of the cyanide groups. The authors did not report any statistical treatment of the data.

In a continuation of their experimental model, Nishimura and Umeda (1979) reported that the difference in chromosomal aberrations induced by the four nickel compounds could not be elucidated by differences in cell incorporation or by uptake differences of labeled precursors of DNA, RNA or protein. The authors were able to state that the differences seemed related to the cumulative toxicity of the compounds; only slight compound differences were observed for treated cells to regain their ability to divide during periods of recovery. The authors speculated that the slight differences in regained ability to divide may have been related to the solubility of the compounds, but suggested that further data collection was necessary to confirm this relationship. Again, no statistical treatment of the data was reported.

Mathur et al. (1978) conducted chromosomal studies on male albino rats treated for a period of 7 and 14 days at doses of 3 and 6 mg Ni/kg. (The nickel was administered intraperitoneally as $NiSO_4$ dissolved in 1 ml of 0.9 percent NaCl. The controls received equal volumes of normal saline.) Nickel treatment did not induce marked chromosomal changes in bone marrow. Although rats administered 6 mg Ni/kg for 14 days showed a few chromatid breaks, according to the authors, these did not differ significantly from controls. (The authors used a Student's t-test; levels of significance for this portion of the study were not reported.) Spermatogonial cells did not show any chromosomal aberrations at either concentrations and durations of nickel exposure.

Unlike other carcinogenic metals, nickel has given consistently negative results for mutagenicity in microbial test systems (Flessel, 1978) such as E. coli (Green et al., 1976) and the rec-assay in B. subtilis (Kanematsu et al., 1980; Nishioka, 1975).

In Nishioka's study, 0.05 ml aliquots of 0.05 M solution of nickel (II) chloride was used in the rec-assay protocol with B. subtilis. No effect was seen on difference in inhibition for the Rec^+/Rec^- strain. Using an improved rec-assay with B. subtilis, Kanematsu et al. (1980) tested for mutagenic activity using 0.05 ml aliquots of 0.005 - 0.5 M solution of nickel chloride ($NiCl_2$) and nickel oxide (NiO, Ni_2O_3). The improved procedures consisted of the insertion of a cold incubation before incubation of plates at 37°C, the cold incubation considerably increasing the assay sensitivity by prolonging the contact period of the compound with non-growing cells. Even with the improved technique, the authors reported negative results for all nickel compounds tested.

Green et al. (1976) used the E. coli reversion fluctuation test to assess nickel (II) chloride mutagenicity over a 5-25 ppm range and found no mutagenic activity for the nickel salt.

In a mutagenicity screening survey using the rec-assay in B. subtilis, Shirasu et al. (1976) reported negative results when testing two nickel-containing pesticides--Baykel, nickel propylenebis (dithiocarbamate) and Sankel, nickel dimethyldithiocarbamate. In subsequent tests, the authors also reported negative results for these two compounds (using one percent solutions) when carrying out reversion-assays on plates using E. coli WP2 and Salmonella TA series of strains; thus, supporting the findings in the above studies that nickel gives negative results in microbial test systems.

5.2.3 Nickel Allergenicity

Nickel dermatitis and other dermatological effects of nickel have been extensively documented in both nickel worker populations and populations at large (Nickel. National Academy of Sciences, 1975). Originally considered to be a problem in occupational medicine, the more recent clinical and epidemiological picture of nickel sensitivity offers ample proof that it is a widespread problem in individuals not having occupational exposure to nickel but encountering an increasing number of nickel-containing commodities in their every-day environment.

5.2.3.1 Clinical Aspects of Nickel Hypersensitivity--Occupational sources of nickel that have been associated with nickel sensitivity include mining, extraction, and refining of the element as well as such operations as plating, casting, grinding, polishing, and preparation of nickel alloys (Nickel. National Academy of Sciences, 1975). Although the frequency of nickel dermatitis has considerably abated owing to advances in both control technology and industrial medicine, it may still persist in electroplating shops (Nickel. National Academy of Sciences, 1975).

Nonoccupational exposure to nickel leading to dermatitis includes nickel-containing jewelry, coinage, tools, cooking utensils, stainless steel kitchens, prostheses, and clothing fasteners. Women appear to be particularly at risk for dermatitis of the hands, which has been attributed to their continuous contact with many of the nickel-containing commodities noted above (Malten and Spruit, 1969).

Nickel dermatitis in nickel miners, smelters, and refiners usually begins as itching or burning papular erythema in the web of the fingers and spreads to the fingers, wrists, and forearms. Clinically, the condition is usually manifested as a papular or papulovesicular dermatitis with a tendency toward lichenification, having the characteristics of atopic, rather than eczematous, dermatitis.

According to Calnan (1956), on the basis of a large number of cases, nickel dermatitis has a unique topographical distribution pattern: (1) primary: areas in direct contact with the element; (2) secondary: spreading of the dermatitis in a symmetrical fashion; and (3) associated: afflicted areas having no relation to contact areas. Furthermore, the affliction may persist some time after removal of obvious sources of exposure.

A clear relationship between atopic dermatitis and that elicited by nickel has been muddied by conflicting reports in the literature. Watt and Baumann (1968) showed that atopy was present in 15 of 17 young patients with earlobe nickel dermatitis, but other workers (Caron, 1964; Marcussen, 1957; Calnan, 1956; Wilson, 1956) have failed to demonstrate any connection between the two disorders. Juhlin et al. (1969) demonstrated elevated immunoglobulin (IgE) levels in atopy patients, while Wahlberg and Skog (1971) saw no significant increases of IgE in patients having nickel and atopic dermatitis histories.

The occurrence of pustular patch test reactions to nickel sulfate has been considered significant in connecting nickel and atopic dermatitis (Becker and O'Brien, 1959). Uehara et al. (1975) have reported that pustular patch test reactions to 5 percent nickel sulfate were regularly produced in patients with atopic dermatitis, but only when applied to areas of papulae, erythema, lichenification, and minimal trauma; such response seldom occurred on normal-appearing skin surface. Furthermore, traumatizing the test areas in control, as well as dermatitic subjects, furnished positive responses. These workers suggest that pustular patch testing is primarily a primary irritant reaction.

Christensen and Möller (1975a) found that of 66 female patients with hand eczema and nickel allergy, 51 had an eczema of the pompholyx type; i.e., a recurring itching eruption with deeply seated fresh vesicles and little erythema localized on the palms, volar aspects, and sides of fingers. Of these, 41 had pompholyx only, while the remainder had at least one of the following additional diagnoses: allergic contact eczema, irritant dermatitis, nummular eczema, or atopic dermatitis. These workers also found that the condition was not influenced by any steps taken to minimize external exposure. Subsequently, these workers (Christensen and Möller, 1975b) discovered that oral administration of nickel in 9 of 12 of the earlier subjects aggravated the condition, while intense handling of nickel-containing objects was without effect. The level of nickel ingested was approximately 5 mg, claimed by the authors to be at the high end of dietary intake in Scandinavian populations.

The role of oral nickel in dermatitic responses has also been demonstrated by Kaaber et al. (1978), who investigated the effect of a low nickel diet in patients with chronic nickel dermatitis presenting as hand eczemas of dyshidrotic morphology. Of 17 subjects in the clinical trial, nine showed significant improvement during a period of 6 weeks on a low nickel diet. Of these nine showing improvement, seven had a flare-up in their condition when placed on a normal diet. Furthermore, there was no correlation apparent between the level of urinary nickel and the degree of improvement following the diet. These authors recommend limitation in dietary nickel as a help in the management of nickel dermatitis. In this connection, Rudzki and Grzywa (1977) described an individual having chronic flare-ups in nickel dermatitis whose chronicity of condition was traced to the nickel content of margarine, Polish margarine having a rather high nickel content, up to 0.2 mg Ni/kg.

While Kaaber et al. (1978) found little correlation between nickel excretion and the status of dermatitis in their patients, Menne and Thorboe (1976) have reported elevated urinary nickel levels during dermatitis flare-ups. deJongh et al. (1978) found limited correlation between plasma nickel level, urinary excretion of nickel, and the clinical activity of the condition in a patient followed during two periods of 5 and 6 weeks each.

Internal exposures to nickel associated with nickel sensitivity and arising from prosthesis alloys have been reviewed (Fisher, 1977; Nickel. National Academy of Sciences, 1975; Samitz and Katz, 1975), and much of these data will only be summarized in this section.

The most common prosthesis alloys are stainless steel or cobalt-chromium (Vitallum), which may contain nickel in amounts up to 35 percent, but generally range between 10-14 percent (Samitz and Katz, 1975).

Instances of allergic reactions, as well as urticarial and eczematous dermatitis, have been attributed to implanted prostheses with resolution of the condition after removal of the devices (Nickel. National Academy of Sciences, 1975; Samitz and Katz, 1975). Apparently, sufficient solubilization of nickel from the surface of the material appears to trigger an increase in dermatitis activity. In support of this, Samitz and Katz (1975) have shown the release of nickel from stainless steel prosthesis by the action of blood, sweat, and saline.

Fisher (1977), in his review, has counseled caution in interpreting the reports and has recommended specific criteria for proof of nickel dermatitis from a foreign body to include evidence of surface corrosion and sufficient corrosion to give a positive nickel spot test.

Determination of nickel dermatitis classically involves the use of the patch test and site response to a nickel salt solution or contact with a nickel-containing object. The optimal nickel concentration in patch test solution is set at 2.5 percent (nickel sulfate). Patch test reactions may be ambiguous in that they can reflect a primary irritation rather than a pre-existing sensitivity (Uehara et al., 1975). Intradermal testing as described by Epstein (1956) has also been employed, but the procedure appears to offer no overall advantage to the conventional method (Nickel. National Academy of Sciences, 1975).

The effect of nickel on lymphocyte transformation and the utility of this phenomenon as an *in vitro* alternative to conventional patch testing with its attendant ambiguity and dermatological hazards merit discussion.

Transformation of cultured human peripheral lymphocytes as a sensitive *in vitro* screening technique for nickel hypersensitivity versus the classical patch testing has been studied in a number of laboratories, and the earlier conflicting studies have been reviewed (Nickel. National Academy of Sciences, 1975). The studies of Svejgaard et al. (1978), Gimenez-Camarasa et al. (1975), Millikan et al. (1973), Forman and Alexander (1972), and Hutchinson et al. (1972) have, however, established the reliability of the technique.

The comparable value of the leukocyte migration inhibition test as an alternative technique remains to be demonstrated conclusively (Macleod et al., 1976; Jordan and Dvorak, 1976; Thulin, 1976).

The induction of nickel sensitivity in human subjects has been claimed by Haxthausen (1936) and Burckhardt (1935). In their subjects, prior sensitivity was not ruled out. Furthermore, the concentration of the sensitizing solution, 25 percent, may easily have induced an irritation response. More recently, Vandenberg and Epstein (1963) successfully sensitized 9 percent (16 of 172) of their clinical subjects.

One area of controversy with regard to nickel dermatitis involves the question of hypersensitivity to groups of metals, i.e., cross sensitivity, and various sides of the issue have been reviewed (Nickel. National Academy of Sciences, 1975). Of particular concern is the existence of hypersensitivity to both nickel and cobalt, as the elements occur together in most of the commodities with which susceptible individuals may come in contact.

The underlying mechanisms of nickel sensitivity presumably include (1) diffusion of nickel through the skin, (2) subsequent binding of nickel ion with protein(s) and other skin components, and (3) immunological response to the nickel-macromolecule complex (Nickel. National Academy of Sciences, 1975). In the section on nickel metabolism, it was noted that penetration of the outer skin layers by nickel does occur. Jansen et al. (1964) found that nickel in complex with an amino acid (D,L-alaline) was a better sensitizer than nickel alone, while Thulin (1976) observed that inhibition of leukocyte migration in 10 patients with nickel contact dermatitis could be elicited with nickel bound to bovine and human serum albumin or human epidermal protein, but not with nickel ion alone. Hutchinson et al. (1975) noted nickel binding to lymphocyte surfaces from both sensitive and control subjects; thus, nickel binding, *per se*, is not the key part of the immunological response (lymphocyte transformation).

5.2.3.2 Epidemiological Studies of Nickel Dermatitis--There are no studies of general populations which relate nickel exposures or levels in tissues and fluids to physiological, subclinical or clinical changes. The studies previously cited do not cover properly designed and executed samples of either total populations or selected population segments which would permit projection of findings to the total population from which subjects were selected. Only some industrially-exposed worker populations have been surveyed or monitored in any statistically adequate manner, and these studies will be reported later in connection with nickel carcinogenesis. The literature on adverse health effects in relation to nickel exposure for the general population is limited to the investigation of nickel dermatitis and nickel sensitivity, with only occasional reports related to other diseases or conditions. These latter are so fragmentary that they will not be considered.

5.2.3.2.1 Nickel sensitivity and contact dermatitis. Nickel dermatitis and other dermatological effects of nickel have been extensively documented in both nickel worker populations and populations at large (Nickel. National Academy of Sciences, 1975). Originally considered to be a problem in occupational medicine, the more recent clinical and epidemiological picture of nickel sensitivity offers ample proof that it is a widespread problem among individuals not having occupational exposure to nickel but encountering an increasing number of nickel-containing commodities in their every-day environment.

There has not been a single population survey using a probability sample to determine the incidence or prevalence of this allergic condition and its clinical manifestation, contact dermatitis. The literature is mostly limited to studies of patient populations, and this provides an unreliable basis for projection to the general population. Clinic populations in specialty clinics are either self-selected and represent individuals who have decided that their condition is severe enough to require medical care or are those who have access to medical care and have been referred to specialty clinics. The perception of need for medical care for specific health problems varies significantly by socio-demographic characteristics. For example, a hairdresser or manicurist with dermatitis of the hands will seek medical care, while a factory worker or clerical worker with the same condition may not do so simply because there are no clients who object. The data presented here, therefore, are of limited value in assessing the distribution of sensitivity in the general population.

Large scale surveys of patient populations were conducted by the International Contact Dermatitis Group (Fregert et al., 1969), The North American Contact Dermatitis Group (1973), and Brun in Geneva (Brun, 1975). Peltonen (1979) and Prystowsky et al. (1979) departed from the practice of surveying patient samples to surveying subjects more representative of the general population, Table 5-11.

All of these studies found that nickel sensitivity is one of the more common ones when standard test kits covering large numbers of substances are used, or when selected smaller numbers of allergens are used. Women always show a higher positive reaction rate than do men, and elicitation of contact history reveals universal exposure to the ubiquitous metal and its compounds.

The North American study permits examination of race as a factor in positive reaction rates. As Table 5-12 shows, blacks have a higher rate than whites, and the females in either racial group have higher reaction rates.

A history of eczema is common in persons with positive reactions. Table 5-11 shows a summary of findings from large scale studies. The finding of particular interest is that nickel sensitivity appears as frequent in "general" population studies as in patient population studies, and it provides more certainty to the finding that large segments of the population, and women in particular, are at risk for this condition.

Table 5-13 shows, for a range of studies, the proportion of nickel sensitives who have a history of eczema of the hand and who reacted in kind to testing. This suggests that nickel sensitivity is by no means a negligible problem for a large proportion of those who exhibit the sensitivity.

Spruit and Bongaarts (1977a) investigated the relationship of nickel sensitivity to nickel concentrations in plasma, urine, and hair and found no association. The role of atopy, either personal or familial, in nickel-sensitive and nonsensitive dermatitis cases was examined by Wahlberg (1975). No differences of rates of personal or familial atopy were found for nickel-sensitive and nonsensitive patients with hand eczema. All cases were ladies' hairdressers; they showed a positive reaction rate of 40 percent to nickel sulfate (5 percent) solution. Wahlberg's finding for atopy are in accord with the earlier work by Caron (1964).

TABLE 5-11. RATES OF POSITIVE REACTORS IN LARGE PATIENT AND POPULATION STUDIES

Study and location	All subjects		Women		Men		Percent nickel sulfate
	number	percent reactors	number	percent reactors	number	percent reactors	
Fregert et al., Europe (1969)	4825	6.7	NA*	9.9	NA	1.8	5.0
North American Contact Dermatitis Group, USA and Canada (1973)	1200	11.2	691	14.9	509	5.5	2.5
Brun, Geneva (1975)	1000	12.2	NA	NA**	NA	NA	3.0
Peltonen, Finland (1979)	980	4.5	502	8.0	478	0.8	5.0 adults 2.5 children
Prystowsky, San Francisco (1979)	1158	5.8	698	9.0	460	0.9	2.5

*NA - not stated
**"higher than men"

TABLE 5-12. NORTH AMERICAN CONTACT DERMATITIS GROUP PATCH TEST RESULTS FOR 2.5 PERCENT NICKEL SULFATE IN 10 CITIES

Subjects		Total No.	Positive Reactions No.	Positive Reactions Percent
Black	Females	79	14	17.7
	Males	64	6	9.3
	Total	143	20	14.0
White	Females	612	89	12.7
	Males	445	22	4.4
	Total	1057	111	10.5
All	Females	691	103	14.9
	Males	509	28	5.5
Total		1200	131	11.2

Source: North American Contact Dermatitis Group (1973).

Spruit and Bongaarts (1977b) and Wahlberg (1975) reported that positive reaction to nickel sulfate occurs at very low dilution levels in some individuals. Wahlberg found 5 of 14 positive reactors sensitive to $\leq$0.039 percent nickel sulfate solution. Spruit and Bongaarts (1977b) found one female patient with a positive reaction when the solution was 10 μg Ni^{++}/ℓ.

The avoidance of contact with nickel suggests itself as an obvious preventive measure. Kaaber et al. (1978) reported encouraging results in attempts to manage chronic dermatitis by reduction of nickel intake via the diet. However, total avoidance of contact with nickel would be extremely difficult, as it is commonly found in articles and substances found in the home and in metals used for jewelry, metal fasteners of clothing, coinage, etc. Some preparations used in hairdressing contain nickel, and consequently hairdressers exhibit nickel dermatitis. The consequences of nickel contact dermatitis seems to vary with the surrounding social factors. Male factory workers appear not to be handicapped by it (Spruit and Bongaarts, 1977b) and continue in their work; hairdressers leave their occupation when they develop dermatitis (Wahlberg, 1975).

TABLE 5-13. HAND ECZEMA IN PERSONS SENSITIVE TO NICKEL

Author	Nickel sensitive	Hand eczema	
		No.	Percent
Bonnevie (1939)	63	32	50.2
Wilson (1956)	85	14	16.5
Calnan (1956)	400	81	20.0
Fisher and Shapiro (1956)	40	16	40.0
Wagmann (1959)	62	22	35.0
Marcussen (1960)	621	272	43.2
Wahlberg and Skog (1971)	53	41	77.3
Cronin (1972)	84	50	60.0
Christensen and Möller (1975a,b)	185	96	52.0
Peltonen (1979)	44	9	20.5

Source: Adapted from Peltonen (1979).

The impact of nickel dermatitis on the health of the total U.S. population cannot be assessed at this time since the prevalence of this condition in the population is not established. Also, there are no data on the range of severity, the consequences, and the costs of the condition.

5.2.3.2.2 Sensitivity to nickel in prostheses. Stainless steel, chrome, and other metal alloys used in prostheses and other surgical devices frequently contain proportions of nickel that have proved to cause reactions in patients ranging from itching to dermatitis to tissue breakdown requiring replacement of the device. The National Academy of Sciences report (1975) lists the following devices and prostheses reported in the literature as associated with adverse reactions to their nickel contents: wire suture materials; metallic mesh for nasal prostheses; heart valves; intrauterine contraceptive devices; batteries for implanted pacemakers; alloys for dental castings and fillings; and orthopedic implants.

The alloys, contrary to general assumption, appear not to be biologically inert and produce adverse reactions in some of the individuals sensitive to nickel. Two cases of cancer in humans at the site of steel plate implantation were reported. These cancers developed 30 years after implantation in both cases. In both cases the alloys of the plates and screws differed and possibly electrolysis and metallic corrosion may have occurred.

eutman and colleagues (1977) reported on metal sensitivity before and after total hip arthroplasty in 212 cases from their orthopedic service in Groningen, The Netherlands. They instituted their study because they noted that the recent literature contained reports of reactions to orthopedic implants which included loosening of total joint prostheses. The authors studied the preoperative sensitivity status of 212 patients scheduled for total hip replacement and followed up these patients to ascertain if sensitivity developed after the insertion. Fourteen patients were sensitive to one or more of three metals tested and eleven of these were sensitive to nickel. The allergens used were those recommended by the International Contact Dermatitis Group, that is, for nickel sensitivity, a 2.5 percent nickel sulfate solution was employed in the patch test. The past experience with metallic appliances for bone surgery was found to be 173 cases without previous experience, 17 cases with less than total joint replacement, 16 with total joint replacement and subsequent loosening and reoperations, and six with stable McKee-Farrar prostheses. Of the eleven nickel-sensitive patients, three had previous implants. Histories of nickel sensitivity showed five cases of eczema due to jewelry or garters and two cases with previous implants where the eczema appeared over the scar tissue of the site of the implant. Four individuals with positive reaction to the nickel allergen did not have a previous history of eczema. In addition, there were five patients with a history of sensitivity but no positive reaction to the patch test.

A second phase of the study consisted of 6 postoperative patch-testing of 66 of the 198 patients that had not exhibited preoperative sensitivity to patch tests. There were 55 women and 11 men with an average age of 69.5 years in this group. Four of these 66 showed metal sensitivity, three to nickel and one to cobalt. This included one woman with a negative preoperative patch test but who had a history of eczema from garters and who was positive on the postoperative patch test. None of the 66, regardless of sensitivity status, had shown pain, loosening of the prosthesis, infection, or skin symptoms during the postoperative period of the study which was approximately two years. This represents a postoperative conversion rate of 6 percent within approximately two years. A sensitivity rate of 4.6 percent to nickel by patch test was found in the 173 patients without previous bone surgery.

Since the publication of the National Academy of Sciences report, additional reports have appeared augmenting the list of items which have created sensitization and symptoms.

This special area of exposure is of grave concern to the medical specialties and the patients involved, and is manageable to some extent by preoperative testing for sensitivity and routine elimination of nickel alloys. The problem does not constitute a risk for the general population and is not related to exposure to nickel in environmental media.

5.2.3.3 Animal Studies of Nickel Sensitivity--Useful experimental animal models of nickel sensitivity have only slowly been forthcoming and only under very specialized conditions.

Nilzen and Wikstrom (1955) reported the sensitization of guinea pigs to nickel via repeated topical application of nickel sulfate in detergent solution. Samitz and Pomerantz (1958), however, have attributed this to local irritation rather than true allergenic response. Samitz et al. (1975) were unable to induce sensitization in guinea pigs using any nickel compound from complexation of nickel ion with amino acids or guinea pig skin extracts.

Wahlberg (1976) employed intradermal injection of nickel sulfate in highly sensitive guinea pigs. The reactions to the challenge were statistically greater than with control animals. Turk and Parker (1977) reported sensitization to nickel manifested as allergic-type granuloma formation. This required the use of Freund's complete adjuvant followed by weekly intradermal injections of 25 μg of the salt after 2 weeks. Delayed hypersensitivity reactions developed in two of five animals at 5 weeks by use of a split-adjuvant method. Interestingly, these workers also observed suppression of the delayed hypersensitivity when intratracheal intubation of nickel sulfate was also carried out on these animals (Parker and Turk, 1978).

5.2.4 Nickel Teratogenicity and Other Reproductive Effects

While it is not a necessary condition of *in utero* toxicity that a toxic element actually enter the fetus, the observation of such entry of an agent helps strengthen a case for overt and subtle teratogenesis. As noted earlier in the discussion on metabolic routes of absorption (Section 4.1.4), nickel crosses the placental barrier in animals and limited data suggests transplacental movement in man.

Teratogenic data for various animal species have been reported for inhalation of nickel carbonyl (Sunderman et al., 1979a, 1980b), and injection of nickel chloride (Gilani and Marano, 1980; Lu et al., 1979; Ferm, 1972). No evidence of teratogenicity was seen in two studies using rats injected with nickel chloride or nickel subsulfide (Sunderman et al., 1978a, 1978b) or rats fed nickel chloride (Nadeenko et al., 1979).

In the Sunderman et al. (1979a) report, two separate studies were described. In the first, pregnant Fischer 344 rats were allowed to breathe either ambient air (controls) or nickel carbonyl on day 7 of gestation for a single 15-minute exposure at a level of 0.3 mg $Ni(CO)_4$/liter in an inhalation chamber. Progeny were studied at birth and for up to 16 weeks. Control animals had no malformed pups in any of the litters (0/8 litters) whereas exposed animals had malformed pups in the majority of litters (6/9 litters) ($p < 0.01$). The live pups/litter were statistically significantly lower in the carbonyl-exposed group ($p < 0.001$, 10.9 in controls versus 8.7 in exposed). Total number of pups with malformations, 22 out of 78 in the exposed group, included 4 with bilateral anophthalmia, 7 with unilateral anophthalmia, 5 with bilateral microphthalmia, 4 with unilateral microphthalmia, and 2 with anophthalmia and microphthalmia. These ophthalmic malformations--lack of eyes or abnormally small eyes--were the only overt teratogenic signs. Furthermore, the rat pups in the exposure group showed significant body weight deficits over controls at both 4 and 16 weeks for males: 41 ± 6 g versus 50 ± 8 g at 4 weeks; 232 ± 15 g versus 267 ± 24 g at 16 weeks, $p < 0.001$.

In the second study, pregnant dams were exposed to ambient air (controls), carbon monoxide (positive controls), or nickel carbonyl at levels of 0.08, 0.16, and 0.30 mg/liter, for 15 minutes at day 7 or 8 of gestation.

In this latter study, where fetuses were examined at day 20 via caesarian section, ophthalmic malformations were seen to have a dose-response relationship. At an exposure of 0.08 mg/liter nickel carbonyl, the number of fetuses with malformations was not statistically different from controls, while levels of 0.16 and 0.30 showed 15 (of 113 total live fetuses) and 29 (of 91 total live fetuses), respectively, with malformations ($p < 0.001$ versus controls). Again, the types of malformations centered on the ophthalmic tract. It appeared that the timing of exposure to nickel carbonyl was crucial in this study. Exposure at day 9 of gestation gave results not different from controls. Since the carbon monoxide control group showed 0 response teratogenically, and CO was employed at levels well above (15X greater) any amounts calculated to arise from $Ni(CO)_4$ decomposition, it could be concluded that nickel carbonyl itself was the teratogen and that this type of teratogenicity appears to be peculiar to nickel carbonyl.

In this same report, the authors drew implications of their results for pregnant women working in areas where nickel carbonyl release may occur. This prompted a response from Warner (1979), who indicated that the Inco refinery at Clydach, Wales, where women were employed intermittently in the early and mid-1900s, has no clinical data suggesting teratogenic behavior. Warner (1979) also pointed out that in the Sunderman et al. (1979a) study, air levels were 3-18 times greater than those measured in the refinery in the late 1950s. No data were given for earlier levels.

In a more recent report, Sunderman et al. (1980b) reported on the teratogenicity and embryotoxicity of nickel carbonyl in Syrian hamsters. Groups of pregnant hamsters inhaled $Ni(CO)_4$ (0.06 mg carbonyl/liter/15 minutes) on days 4, 5, 6, 7 or 8 of gestation. Animals were sacrificed on day 15 of gestation and the fetuses were examined for evidence of malformations. For exposure on days 4 or 5 of gestation, the proportion of litters with malformed fetuses was 33 percent and 24 percent respectively, versus 0 percent in control litters ($p < 0.05$). The malformations in affected litters included 7 fetuses with exencephaly, 9 with cystic lung, one with exencephaly plus fused rib, and one with anophthalmia plus cleft palate. Exposure at day 6 or 7 of gestation yielded a much lower incidence of malformations: one fetus with fused ribs and 2 fetuses with hydronephrosis. Of interest in this study is the fact that the micro- and anophthalmia seen in rats exposed in utero was not seen in hamsters, the latter showing exencephaly and cystic dysplasia of pulmonary parenchyma.

Ferm (1972), in a comprehensive study of the mammalian teratology of metals, reported that nickel (II) acetate at a level of 30 mg/kg injected intravenously into pregnant golden hamsters at day 8 of gestation induced "a few general malformations" in surviving embryos. No further details were reported as to the nature of the malformations or the statistical significance of their occurrence. Embryotoxicity data, however, was provided for a nickelous acetate given via the above protocol, using dosing levels of 2, 5, 10, 20, 25 and 30 mg/kg. The corresponding number of resorbed embryos at these levels were 0, 1, 22, 10, 59 and 33, respectively, for corresponding total embryo counts of 24, 22, 56, 55, 68 and 33, respectively. The number of surviving abnormal embryos at these dosing levels were 2, 1, 2, 1, 4 and 0, the last figure arising from the fact that there were no survivors at the 30 mg/kg dose. The rate of embryo resorption appeared to be dose-dependent in a more consistent manner than were the numbers showing malformations.

Lu et al. (1979) have described the teratogenic effects of nickel (II) chloride in mice. Pregnant mice of the ICR strain were given a single i.p. injection of nickel chloride at a level of 1.2, 2.3, 3.5, 4.6, 5.7, or 6.9 mg Ni/kg at days 7-11 gestation. Abnormalities observed in fetuses, ranked according to decreasing frequency of type of anomaly across the treatment groups, were: rib and/or vertebral fusion; cleft palate; open eyelid; club foot; ankylosis of extremity, cerebral hernia; exencephaly; micromelia and acephaly. The five control groups for days 7, 8, 9, 10 and 11 of gestation showed 0 percent abnormalities, except for day 9 where the control frequency was 1.7 percent. The percent frequency of abnormalities was generally seen to increase with increasing dosage at a given period of gestation and to be greatest at day 8 or 9 for a given dosing.

This study clearly showed a dose-response relationship for teratogenesis and level of nickel (II) administration. At day 9, for example, the frequency for abnormalities in the 1.2, 2.3, 3.5, 4.6, 5.7 mg/kg treatment groups was 4.9, 13.0, 21.4, 50.8 and 69.4 percent, respectively, with an observed 100 percent mortality in the 6.9 mg/kg exposure group. A similar dose-response relationship between percentage of fetal deaths and nickel dosing levels was recorded. It should be noted that the dosing levels represented approximately one-tenth of the LD-50 dose for the mothers.

Gilani and Marano (1980) demonstrated teratogenic effects of nickel chloride in developing chick embryos receiving levels of 0.02 to 0.7 mg/egg via injection into the air sacs at days 0-4 of incubation. Control eggs received the same volume (0.1 ml) of saline vehicle. All embryos were studied at day 8. Malformations observed included exencephaly, everted viscera, short and twisted neck, deformed limbs, microphthalmia and hemorrhage.

Of the embryos that survived the injection on day 0 (at all dose levels of nickel (II) ion), 48 percent had gross malformations, while from injections at days 1, 2, 3 and 4 the respective percentages of gross malformations were 50, 66, 16 and 22, indicating that embryogenesis at day 2 was most vulnerable to nickel ion's teratogenic potential. Saline-injected controls showed a malformation incidence of 2 percent.

By contrast, Sunderman et al. (1978a) studied the teratogenic potential of nickel (II) chloride and nickel subsulfide when injected into pregnant rats on day 8 of gestation, using single i.m. dosing of 16 mg/kg nickel chloride and 80 mg/kg nickel subsulfide and found no evidence for malformations among the fetuses.

5.2.4.1 Generalized Embryotoxicity of Nickel Compounds--In all of the studies cited above which showed teratogenic effects, generalized *in utero* toxicity ranging from reduced fetus weights to fetal mortality was also reported.

In the Sunderman et al. (1979a) study demonstrating the teratogenicity of nickel carbonyl for rat fetuses when pregnant rats were exposed to a 15-minute inhalation interval, 0.30 mg/liter, the mean number of live pups/litter in the exposed groups was 8.7 versus 10.9 in control animals, statistically signficant at $p < 0.001$. Weights of live fetuses were significantly reduced relative to control weights, $p < 0.01$ at exposure levels of 0.08, 0.16 and 0.30 mg/liter, 15-minute interval, in a second study (Sunderman, 1979a).

Ferm (1972) found that nickelous acetate, when given as i.v. single doses to pregnant hamsters, resulted in decreases in the numbers of surviving embryos and increases in embryo resorption with a dose-response relationship over the range 2-30 mg/kg, as noted above (Section 5.2.4).

In the study of Lu et al. (1979), not only were the dose-response relationships for malformations, but also for the number of resorbed fetuses and fetal mortality when nickel was given as a single i.p. injection of the chloride to pregnant mice over the dosing range 1.2-6.9 mg/kg and from the 7th to 11th day of gestation. For example, exposure at day 9 of gestation gave the following fetal death percentages for various exposures: 1.2 - 4.1; 2.3 - 11.1; 3.5 - 35.9; 4.6 - 77.7; 5.7 - 71.1; and 6.9 mg/kg - 100 percent. Live fetus weights were signficantly reduced at an exposure level as low as 3.5 mg/kg on day 8 of gestation ($p < 0.05$, versus controls) and at higher doses the level of significance was even greater ($p < 0.01$ versus controls).

In the study of Sunderman et al. (1980b), where pregnant Syrian hamsters were exposed to nickel carbonyl by inhalation (0.06 mg/liter, 15 minutes) on day 5 of gestation, the neonatal mortality was increased by day 4 postpartum. Live pup numbers averaged 7.6 in exposed litters, versus 9.6 in control litters ($p < 0.01$).

In the chick embryo study of Gilani and Marano (1980), a dose-response relationship was seen for embryo mortality at day 0, 1, 2 and 3 when nickel chloride was injected into eggs at levels from 0.02-0.7 mg/egg. For example, on day 1 of incubation the percentages of viable embryos relative to injected nickel levels were: 0.02 - 46; 0.05 - 46; 0.08 - 17; 0.1 - 17; 0.4 - 8; 0.7 mg - 4 percent. On the same day the control value was 92 percent demonstrating a statistically significant difference between treated and control eggs ($p < 0.01$).

Several studies have explored the effect on progeny of feeding nickel compounds to pregnant animals.

Phatak and Patwardhan (1950) placed breeding pairs of albino rats on diets containing 250, 500 or 1,000 ppm nickel and in the form of dispersed metallic nickel catalyst, nickel carbonate or nickel soap at eight weeks prior to breeding and continued through gestation, delivery and lactation. No statistically significant effect was seen on litter size or newborn body weights.

Ambrose et al. (1976) reported data for a three-generation study of albino rats fed nickel sulfate in rat chow at levels of 250, 500 and 1,000 ppm of nickel. After 11 weeks of nickel-in-diet exposure, the females were bred to males having the same dietary regimen. The first generation consisted of two groups of offspring, F1a and F1b, derived from the remating of the parent generation. For the second generation study, breeding pairs from dams and sires exposed to nickel in F1b were then placed on the same diet. Progeny from this generation were carried through the same protocol; subsequently, all generations were comprised of two groups of offspring.

The authors noted increased fetal mortality in the first generation at all dietary levels of nickel; however, no statistical analysis was performed on the stillbirth data. Decreased body weights of weanlings on the 1,000 ppm nickel diet were noted in all generations. In addition, nickel exposure to this highest level significantly reduced the life span of rats followed over a 2-year interval ($p = 0.05$). This study poses some interpretive problems, however. Stillborn effects were only noted in the first generation; however, it is possible that the absence of stillbirths in the second and third generations represented a selection process that occurred in the first generation. That is, all of the vulnerable members of the litter died in the first generation, and the survivors selected for further breeding represented a selection for resistance to _in_ _utero_ effects of nickel. It should also be noted that no clear dose-response relationship between exposure level and number of stillbirths were consistently seen for both Fla and Flb offspring, this relationship only being apparent in Flb.

Schroeder and Mitchener (1971) reported that nickel ion (sulfate) in drinking water at a level of 5 ppm over lifetime resulted in increased numbers of runts and increased neonatal mortality in all 3 generations of a 3-generation study. However, a number of design problems exist with this particular study. Diets were deficient in a number of trace elements, animals were not randomly assigned to experimental groups, nor were effects assessed on a litter versus individual animal basis. Furthermore, these workers could not duplicate the results in a repeat study according to their final progress report (Schroeder and Nason, unpublished).

5.2.4.2 _Gametotoxic Effects of Nickel_--Several studies have reported the gametotoxic effects of injected nickel (II) salts in animals, specifically with respect to spermatogenesis and testicular injury (Von Weltschewa et al., 1972; Hoey, 1966; Kamboj and Kar, 1964).

Kamboj and Kar (1964) gave nickel nitrate either as a single intratesticular injection, 0.08 mMoles/kg (~ 5.0 mg/kg) into albino rats or as 30 s.c. injections over 30 days for a total of 5.0 mg/kg in Swiss mice. Significant reduction in testicular weights was observed by day 7 in rats and by day 2 in mice. In rats, damage to the seminiferous epithelium with exfoliation and cell lipes was seen, such injury being transitory with interstitial regeneration occurring with time. Spermatozoa were not affected. In the mice given repeated s.c. injections, there was shrinkage of seminiferous tubules and arrest of spermatogenesis at the primary spermatocyte or spermatogonal stages, with no effect on testicular interstitium. Thus, there was a species difference in the site of effect of nickel in testes.

Repeated s.c. administration of nickel ion (Hoey, 1966) as the sulfate (2.4 mg Ni/kg, single or multiple injections) in male rats produced such testicular effects as shrinkage of central tubules, hyperemia of intertubular capillaries, and disintegration of spermatozoa in testicular tissue as early as 18 hours after a single dose. Multiple dosing produced disintegration of spermatocytes and spermatids with destruction of Sertoli cells. Such effects were noted to be reversible.

Von Weltschewa et al. (1972) noted inhibition of spermatogenesis in rats fed nickel sulfate in their diets, 25 mg/kg, for a total of 120 days. In addition, a reduction was seen in the number of tubule basal cells and in the number of spermatozoa-containing tubules. By the end of the 120-day oral exposure period, these animals showed total obliteration of fertility.

No gametotoxic effects have been reported in man.

5.2.5 Other Toxic Effects of Nickel

5.2.5.1 Respiratory Effects of Nickel--The acute effects of $Ni(CO)_4$ on the lung in man and experimental animals were summarized earlier (Section 4.1). Little data are available on the chronic respiratory effects of this agent, except for one case described by Sunderman and Sunderman (1961b) in which a subject exposed to low levels of the carbonyl developed asthma and Löffler's syndrome, a condition characterized by fever, cough, breathlessness, anorexia, weight loss and associated with eosinophilia and granulomatous tissue.

Russian workers (Sushenko and Rafikova, 1972; Kucharin, 1970; Tatarskaya, 1960) have observed chronic rhinitis and nasal sinusitis in workers engaged in nickel electroplating operations where chronic inhalation of nickel aerosols, such as nickel sulfate, had occurred. Associated findings commonly encountered were anosmia and nasal mucosal injury including nasal septum perforation. Asthmatic lung disease in nickel plating workers has been documented by McConnell et al. (1973) and Tolat et al. (1956).

Adverse effects in animals by inhalation of several forms of nickel have been reported. Bingham et al. (1972) exposed rats to aerosols of both soluble (as the chloride) and insoluble (as the oxide) nickel at levels in the region of those acceptable for human industrial exposure. Hyperplasia of bronchiolar and bronchial epithelium with peribronchial lymphocytic infiltrates was seen. Port et al. (1975) noted that intratracheal injection of a suspension of nickel oxide (5 mg, < 5 μm) into Syrian hamsters first treated with influenza A/PR/8 virus 48 hours previously, significantly increased mortality versus controls. Surviving animals at this dosing and lesser doses showed mild to severe acute interstitial infiltrate of polymorphonuclear cells and macrophages several weeks later. Additional pathological changes included bronchial epithelial hyperplasia, focal proliferative pleuritis and adenomatosis.

A number of studies have involved the cellular toxicity of nickel compounds as they relate to the incidence of infections in the respiratory tract, particularly the impairment of alveolar macrophage activity (Castronova et al., 1980; Johansson et al., 1980; Aranyi et al., 1979; Adkins et al, 1979; Graham et al, 1975; Waters et al., 1975).

At 1.1 mM nickel ion, rabbit alveolar macrophages show no morphological evidence of injury but apparently lose the ability for phagocytosis (Graham et al., 1975). At 4.0 mM, cell viability is reduced to approximately 50 percent of controls (Waters et al., 1975).

Aranyi et al. (1979) demonstrated that alveolar macrophage viability, total protein and lactate dehydrogenase activity were significantly affected when nickel oxide was adsorbed into fly ash ranging in size from less than 2 μm to 8 μm. The effect increased with increased particle loading of NiO and decreased particle size.

5.2.5.2 Endocrine Effects of Nickel--In different experimental animal species, nickel (II) ion has been shown to affect carbohydrate metabolism. Bertrand and Macheboeuf (1926) reported that the parenteral administration of nickel salts antagonized the hypoglycemic action of insulin. Later workers (Horak and Sunderman, 1975a and 1975b; Freeman and Langslow, 1973; Clary and Vignati, 1973; Kadota and Kurita, 1955) observed a rapid, transitory hyperglycemia after parenteral exposure of rabbits, rats, and domestic fowl to nickel (II) salts. In several reports, Horak and Sunderman (1975a; 1975b) noted the effects of nickel (II) on normal, adrenalectomized, and hypophysectomized rats. Injection of nickel chloride (2 or 4 mg/kg) produced prompt elevations in plasma glucose and glucagon levels with a return to normal 2-4 hours afterwards, suggesting that hyperglucagonemia may be responsible for the acute hyperglycemic response to divalent nickel (Horak and Sunderman, 1975a). Nickel had the most pronounced hyperglycemic effect when this element was studied versus effects of other ions given in equimolar amounts, while concurrent administration of insulin antagonized the hyperglycemic effect (Horak and Sunderman, 1975b). Kadota and Kurita (1955) observed marked damage to alpha cells and some degranulation and vacuolization of beta cells in the pancreatic islets of Langerhans. Ashrof and Sybers (1974) observed lysis of pancreas exocrine cells in rats fed nickel acetate (0.1 percent).

Human endocrine responses to nickel have been poorly studied, although Tseretili and Mandzhavidze (1969) found pronounced hyperglycemia in workmen accidentally exposed to nickel carbonyl.

Nickel apparently has an effect on the hypothalamic tract in animals, enhancing the release of prolactin-inhibiting factor (PIF) thereby decreasing the release of prolactin from bovine and rat pituitary glands (La Bella et al., 1973a). Furthermore, intravenous administration of small amounts of nickel to urethane-anesthetized, chlorpromazine-treated rats produces significant depression of serum prolactin without any affect on growth hormone or thyroid-stimulating hormone. The in vitro release of pituitary hormones other than PIF have been demonstrated for bovine and rat pituitary (La Bella et al., 1973b).

Dormer and coworkers (1973; 1974) have studied the in vitro effects of nickel on secretory systems, particularly the release of amylase, insulin, and growth hormone. Nickel (II) was seen to be a potent inhibitor of secretion in all three glands: parotid (amylase), islets of Langerhans (insulin), and pituitary (growth hormone). Inhibition of growth hormone release at nickel levels comparable to those which La Bella et al. (1973b) observed to enhance release, may reflect differences in tissue handling prior to assay. Dormer et al. (1973) suggested that nickel may block exocytosis by interfering with either secretory-granule migration or membrane fusion and microvillus formation.

Effects of nickel on thyroid function have been noted by Lestrovoi et al. (1974). Nickel chloride given orally to rats (0.5-5.0 mg/kg/day, 2-4 weeks) or by inhalation (0.05-0.5 mg/m^3) significantly decreased iodine uptake by the thyroid, such an effect being more pronounced for inhaled nickel.

5.2.5.3 Renal Effects of Nickel--Nickel-induced nephropathy in man or animals has not been widely documented. Acute renal injury with proteinuria and hyaline casts were observed by Azary (1879) in cats and dogs given nickel nitrate. Pathological lesions of renal tubules and glomeruli have been seen in rats exposed to nickel carbonyl (Hackett and Sunderman, 1967; Sunderman et al., 1961; Kincaid et al., 1953). Gitlitz et al. (1975) observed aminoaciduria and proteinuria in rats after single intraperitoneal injection of nickel chloride, the extent of the renal dysfunction being dose-dependent. Proteinuria was observed at a dose of 2 mg/kg, while higher dosing occasioned aminoaciduria. Ultrastructurally, the site of the effect within the kidney appears to be glomerular epithelium. These renal effects were seen to be transitory, abating by the fifth day.

In man, nephrotoxic effects of nickel have been clinically detected in some cases of accidental industrial exposure to nickel carbonyl (Carmichael, 1953; Brandes, 1934). This takes the form of renal edema with hyperemia and parenchymatous degeneration.

5.2.5.4 Miscellaneous Toxic Effects of Nickel--Nickel compounds appear to possess low neurotoxic potential save for fatal acute exposures to nickel carbonyl (National Institute for Occupational Safety and Health, 1977b; Nickel. National Academy of Sciences, 1975). Neural tissue lesion formation in the latter case is profound, including diffuse punctate hemorrhages in cerebral, cerebellar, and brain stem regions, degeneration of neural fibers, and marked edema.

Intrarenal injection of nickel subsulfide in rats elicits a pronounced erythrocytosis (Hopfer et al., 1980; Hopfer and Sunderman, 1978; Morse et al., 1977; Jasmin and Riopelle, 1976), the erythrogenic effect being apparently unrelated to the carcinogenicity of the compound (Jasmin and Riopelle, 1976). Morse et al. (1977) showed that the erythrocytosis is dose-dependent, is not elicited by intramuscular administration and is associated with marked erythroid hyperplasia of bone marrow. Hopfer and Sunderman (1978) observed a marked inhibition of erythrocytosis when manganese dust was co-administered.

5.3 INTERACTIVE RELATIONSHIPS OF NICKEL WITH OTHER FACTORS

Both antagonistic and synergistic interactive relationships have been demonstrated for both nutritional factors and other toxicants. (Carcinogenic interactions have been previously discussed in Section 5.2.1.)

Co-administration of high doses of vitamin C to the weanling rat offset the effects of oral nickel exposure on growth rate, as well as the activity of certain enzymes, such as liver and kidney succinic dehydrogenase and liver glutamic-oxaloacetic transaminase (Chatterjee et al., 1980).

According to Hill (1979), dietary protein antagonizes the effect of dietary nickel (as the chloride, 400 or 800 ppm) on retarding growth in chicks over the range of 10-30 percent protein.

Ling and Leach (1979) studied element interaction in diets containing 300 mg/kg of nickel and 100 mg/kg of iron, copper, zinc, and cobalt. Indices of toxicity were growth rate, mortality, and anemia. The lack of interaction among these elements and nickel is in contrast to a protective effect of nickel for the adverse effects of copper deficiency (Spears and Hatfield, 1977). Presumably, the existence of any interactive mechanism is overwhelmed at large levels of agents employed in the former study.

According to Nielsen (1980), there is a nutritional interaction between iron and nickel in the rat which depends on the state (valence) and level of iron in the diet. Nickel supplementation offset reduced hemoglobin and hematocrit values in iron-deprived rats when the ferric ion was employed, but less so when divalent-trivalent iron mixtures were used. This author postulates that the enhanced absorption of the trivalent iron was directly related to nickel.

Divalent nickel appears to antagonize the digoxin-induced arrythmias in the rat, rabbit, and guinea pig in both intact, as well as, isolated hearts, doing so by either binding competition with calcium ion at cell membranes or provoking an increase in malic and oxaloacetic acid activity (Prasad et al., 1980).

Nickel ion combined with benzo(a)pyrene enhanced the morphological transformation frequency in hamster embryo cells over that seen with either agent used alone (10.7 percent, verses 0.5 percent and 0.6 percent for nickel and benzo(a)pyrene, respectively) at levels of 5 μg/ml nickel salt and 0.78 μg/ml benzo(a)pyrene. Futhermore, in a mutagenesis system using hamster embryo cells, as described by Barrett et al. (1978), a co-mutagenic effect between nickel sulfate and benzo(a)pyrene has also been observed (Rivedal and Sanner, 1980; 1981). These observations, supported by co-carcinogenic effects between nickel compounds and certain organic carcinogens

(Toda, 1962; Maenza et al., 1971; Kasprzak et al., 1973), are of considerable importance in evaluating the enhancing effect of cigarette smoke on the incidence of lung cancer in nickel refinery workers (Kreyberg, 1978).

6. NICKEL AS AN ESSENTIAL ELEMENT

There is a growing body of literature that establishes an essential role for nickel, at least in experimental animals (Sunderman, 1977; Spears and Hatfield, 1977; Nielsen, 1976; Nickel. National Academy of Sciences, 1975; Nielsen and Sandstead, 1974).

Mertz (1970) has spelled out criteria for essentiality of trace elements as micronutrients, and this discussion will focus primarily on one of the most critical of these: demonstration of specific deficiency-related syndromes which are prevented or cured by the element alone.

Earlier workers in trace-element nutritional research could not demonstrate any consistent effects of nickel deficiency (Spears and Hatfield, 1977; Nickel. National Academy of Sciences, 1975) owing in part to the technical difficulties of controlling nickel intake because of its ubiquity. Later workers have demonstrated adverse effects of nickel deprivation in various animal models.

Nielsen and Higgs (1971) have shown a nickel-deficiency syndrome in chicks fed nickel at levels of 40-80 ppb (control diet: 3-5 ppm) characterized by swollen hock joints, scaly dermatitis of the legs, and fat-depleted livers. Sunderman et al. (1972b) observed ultrastructural lesions such as perimitochondrial dilation of rough endoplasmic reticulum in hepatocytes of chicks fed a diet having 44 ppb nickel. Nielsen and Ollerich (1974) also noted hepatic abnormalities similar to those reported by Sunderman et al. (1972b). Nickel is also essential in swine nutrition. Pigs fed a diet having 100 ppb nickel showed signs of decreased growth rate, impaired reproduction, and rough hair coats (Anke et al., 1974).

Growth responses to nickel supplementation have also been reported for rats (Nielsen et al., 1975; Schnegg and Kirchgessner, 1975a; Schroeder et al., 1974). Rats maintained on nickel-deficient diets through three successive generations showed a 16 percent and 26 percent weight loss in the first and second generations, respectively, when compared to nickel-supplemented controls (Schnegg and Kirchgessner, 1975a).

Effects on reproduction have been documented in rats (Nielsen et al., 1975) and swine (Schnegg and Kirchgessner, 1975a; Anke et al., 1974), mainly in terms of increased mortality during the suckling period (rats) and smaller litter size (both species).

Nickel appears to be essential also for ruminant nutrition (Spears and Hatfield, 1977). Spears and Hatfield (1977) demonstrated disturbances in metabolic parameters in lambs maintained on a low-nickel diet (65 ppb), including reduced oxygen consumption in liver homogenate preparations, increased activity of alanine transaminase, decreased levels of serum proteins, and enhanced urinary nitrogen excretion. In a follow-up study, Spears et al. (1978) found that these animals had significantly lower microbial urease activity.

Schnegg and Kirchgessner (1976; 1975b) demonstrated that nickel deficiency leads to reduced iron content in organs and iron deficiency anemia, resulting from markedly impaired iron absorption.

Nickel also appears to adhere to other criteria for essentiality (Mertz, 1970) e.g., apparent homeostatic control, and partial transport by specific nickel-carrier proteins (see Metabolism section). Furthermore, Fishbein et al. (1976) have reported that jackbean urease is a natural nickel metalloenzyme. It is possible that rumen bacterial urease may also have a specific nickel requirement (Spears et al., 1977). In this connection, Mackay and Pateman (1980) have found that a mutant strain of Aspergillis nidulans, which is urease-deficient, requires nickel (II) for restoration of urease-activity. In particular, the strain carrying a mutation in the ure-D locus was responsive to nickel.

7. HUMAN HEALTH RISK ASSESSMENT FOR NICKEL

Assessment of the risk posed by nickel to public health in the United States entails consideration of two general facets of the issue: sources of exposure relevant to U.S. populations at large and population response.

Two obvious questions about the exposure aspects of nickel are: (1) What are the environmental sources of nickel in the United States? (2) What are the various routes by which nickel enters the body?

Nickel, in common with other metallic elements, is a multimedia contaminant. Thus, one needs to have some idea of the comparative contributions to human exposure by all the various routes before one can assess the relative significance of any given avenue of intake. A second complicating factor is the impact of a primary route of environmental entry on other compartments of the environment. For example, to what degree does airborne nickel contribute to contamination of water and soil via fallout?

Some aspects of the problem of human population response to nickel include: (1) the relevant human biological and pathophysiological responses to nickel; (2) subgroups of the U.S. population that can be identified as being at particular risk to effects of nickel by virtue of either exposure setting or some physiological status imparting heightened vulnerability; and (3) the magnitude of the risk to these subgroups in terms of the numbers exposed as can best be determined by available population data.

7.1 AGGREGATE HUMAN INTAKE OF NICKEL

The general population of the United States receives its major external exposure to nickel via ingestion, inhalation, and skin contact. While estimates of the daily dietary intake of nickel vary, a range of 300-600 μg nickel/day on the basis of composite diet analysis appears to exist in the United States. Fecal nickel analysis, a more accurate measure of dietary nickel intake, suggests about 300 μg nickel/day. Assuming an absorption of 1-10 percent, up to 60 μg nickel/day may be taken up from the gastrointestinal tract.

For the inhalation route, a nonsmoking urban resident exposed to a mean air level of nickel of about 10 ng/m^3 would take in 0.2 μg nickel, assuming a daily ventilation rate of 20 m^3. Of this amount, some fraction would be absorbed, depending on the size of the nickel-containing particulate. Even with the assumption of 100 percent absorption, the relative amount of inhaled nickel absorbed into the blood stream would be minor compared to dietary nickel.

Cigarette smokers probably have a markedly increased nickel intake from the respiratory tract. As noted in Chapters 3 and 4, individuals smoking two packs of cigarettes a day would inhale 1-5 mg of nickel per year or about 3-15 µg nickel daily (National Academy of Sciences, 1975). Considering that (1) better than 80 percent of cigarette nickel in mainstream smoke is in gaseous, rather than particulate form (Stahly, 1973; Szadkowski et al., 1970; Sunderman and Sunderman, 1961a) and (2) inhalation of gaseous nickel compounds is likely to result in greater nickel deposition in the pulmonary parenchyma (National Academy of Sciences, 1975), it would not be unreasonable to assume the strong likelihood of absorption of a major portion of the daily cigarette amount (1.5-7.5 µg for 50 percent absorption).

It would also not be unreasonable to assume for a certain portion of the general populace, that inhalation of passive smoke may constitute a possible exposure route, the magnitude of which is presently unknown and, therefore, cannot be quantifiably figured into aggregate nickel intake.

Average drinking water nickel values are about 5 µg/ℓ. Assuming a typical daily consumption of 2.0 liters, about 10 µg of nickel may be ingested. Assuming 1-10 percent absorption, 0.1-1.0 µg is absorbed.

It is not possible to make any quantitative statements about the amounts of systemic or percutaneous absorption of nickel via external contact with nickel-containing commodities by the general population.

The aggregate daily absorption from all sources is approximately 3-60 µg nickel, with most of this amount coming from the diet.

7.2 SIGNIFICANT HEALTH EFFECTS OF NICKEL FOR HUMAN RISK ASSESSMENT

A variety of *in vivo* adverse effects of nickel have been documented in experimental animals and man and are described in Chapter 5. It should be kept in mind that these studies involved rather high levels of exposure, employed parenteral administration of the nickel agent in a number of cases, and in some cases employed nickel in forms which may not be relevant to general population exposure and are of more concern in occupational settings.

Acute exposure of man to nickel is mainly of concern in workplaces where nickel carbonyl or nickel dusts are present at high levels. Here, inhalation is the main route of entry into the body and the lung is the critical organ, although in cases of accidental exposure to high levels of nickel carbonyl, other systems such as the central nervous system may also be involved. Most of what is known about acute exposure effects is based upon nickel carbonyl inhalation. Aside from accompanying weakness and hyperpnea, symptomatology from such exposure strongly resembles that of viral pneumonia.

Chronic exposure to nickel compounds is of more concern in both occupational and general population groups. In nickel workers, an extensive literature points to a significantly increased nasal and lung cancer risk, as well as noncarcinogenic effects, such as skin disorders, inflammation of the upper respiratory tract, and possible renal dysfunction. In workers chronically exposed to nickel, the route of intake is mainly by inhalation, although percutaneous absorption figures in skin disorders.

The major problem posed by nickel for the U.S. population at large, as can best be determined at present, is nickel hypersensitivity. Nickel reactions, originally equated with occupational diseases, appear today with much greater frequency, especially among women. Environmental exposure, mainly via contact with many nickel-containing commodities, is responsible for a preponderance of such reactions. Data cited in Chapter 5 also suggest that nickel could play a role in altering defense mechanisms against xenobiotic agents in the respiratory tract, leading to heightened risk for respiratory tract infections.

The possible role of certain nickel compounds as co-carcinogens in respiratory cancer is suggested by animal studies but remains to be conclusively demonstrated.

Any discussion of health risk assessment of nickel must consider two key points regarding the effects relevant for human populations: (1) the reversibility or irreversibility of a given health effect if the subject is removed from exposure to nickel and (2) the relative significance of a given effect in impairing the individual's systemic well-being or ability to fully function.

If one takes clinically manifested nickel sensitivity in the form of contact dermatitis or other skin disorders as the effect of nickel most germane to chronic exposure of populations at large, it would appear that reversibility exists in one sense, i.e., avoiding obvious exposure to nickel-containing material may ameliorate the immediate symptoms. To the extent that a nickel-hypersensitized individual will suffer a flare-up of symptoms when exposed again, one can argue that the symptomatology may be reversible but that the underlying condition is irreversible.

The extent to which nickel hypersensitivity as manifested in skin disorders is an adverse health effect depends on both the severity of the condition and other factors, for example, occupational status. While a condition such as nickel contact dermatitis may not be life-threatening, severe cases of nickel-induced skin disorders can have a significant impact in limiting the daily activities of individuals and can predispose those afflicted to further complications such as skin infections. Also, for such occupational groups as hairdressers, chronic skin disorders induced by nickel can have a marked impact on continued livelihood, particularly in situations involving public contact.

Evidence was presented in Chapter 6 pointing to nickel as an essential element, at least in animals. Nickel deficiency has been associated with reduced growth, impaired reproduction and the induction of anemia by interfering with iron absorption. Further data in support of essentiality includes apparent homeostatic control of nickel in a number of animal species and the existence of nickel carrier proteins in man and rabbit.

7.3 DOSE-EFFECT AND DOSE-RESPONSE RELATIONSHIPS OF NICKEL

Attempts to quantify the health impact of nickel on man with reference to potential effects on the U.S. population as a whole are discussed in this section, with emphasis on data for chronic exposure. Unlike the relevant literature available for elements such as cadmium, lead, and mercury on dose-response relationships, the corresponding information for nickel is sparse. In large measure, this is due to the perception of nickel both as mainly a problem in occupational medicine and as having overall lower toxicity with regard to chronic exposure of non-occupational populations.

An approach to assessing dose-effect, dose-response relationships for nickel or any agent in man can be framed in the form of several questions:

(1) How do the various levels of external exposure--nickel in air, food, water--quantitatively translate to reliable internal indices of

exposure such as blood nickel, urinary nickel, nickel in hair, autopsy tissue?

(2) How do the levels of nickel in these internal indices of exposure relate to the eliciting and the graded severity of critical effect in the critical tissue?

(3) Is the information in answer to questions (1) and (2) sufficient to permit either modeling or statistical refinement of the data, to estimate what fraction of a study population is apt to develop a particular health effect at a given level of external exposure?

7.3.1 Indices of Exposure

Taken collectively, occupational and limited nonoccupational group studies indicate that both urinary and serum nickel levels generally reflect the intensity of recent or ongoing exposures. Nickel in these media rise rapidly with increases in external exposure and rapidly decrease in levels with reduced external exposure. Nickel workers usually show higher serum and urine levels than control groups. While hair nickel levels may be of value in elucidating a history of chronic or episodic acute nickel exposure, various technical problems associated with this medium have limited its wide acceptance as an index in assessing dose-effect, dose-response relationships.

Norseth (1975) attempted to calculate the degree of correlation between nickel levels in physiological media (urine in this case) and workplace exposure. For welders, he found that the exposure/excretion ratios were well correlated as a group (correlation coefficient of 0.85), but that urinary nickel was poorly correlated with any individual's exposure. Norseth (1975) also observed that welders had exposure/excretion ratios which were similar to those of nickel roasters and smelters, suggesting exposure to similar forms of nickel.

The data for nickel levels in blood, urine, hair, and other tissue in "normal" populations must be viewed with great caution for several reasons. The definition of "normal" population varies enormously from study to study. In many cases, it is defined as "not occupationally exposed" without provision of criteria for such definitions. Studies using patients or other subjects as controls do so on the basis of freedom from a particular disease or condition, rather than on general health status. Since nickel levels are affected by a number of stresses, this is an important, yet overlooked consideration. In some studies, population selection may also have been done to primarily assess exposure to other pollutants, and group stratification based on gradients for other pollutants may not necessarily reflect nickel exposure differences since sources of nickel may not always be the same as those of other selected contaminants. In addition, it should be noted that smoking status of tested individuals has not been systematically considered in many of these studies. Finally, the quality of analytical methodology varies significantly for nickel, both with techniques and with time, so that earlier studies may not have yielded levels which are as reliable as more recent findings (Adams and co-workers, 1978; National Academy of Sciences, 1975; Lewis and Ott, 1970).

"Normal" levels of nickel in blood of various population groups in the United States and elsewhere are presented in Table 7-1. The table is a compilation of more recent data which were obtained with the relatively more reliable method of atomic absorption spectrometry. Generally, serum or plasma values are less than 1.0 µg/dl, or 10 µg/liter.

Age and sex do not appear to be associated with nickel blood levels, as authors frequently report mean values for total groups only because they have found no significant differences by age or sex. Other variables such as race, residence, and geographic location similarly cannot be evaluated, and further, there are no data for "unacculturated" populations who are not exposed to industrial pollution.

The only study addressing the question of differences in mean blood nickel levels for normal populations living in environments with different degrees of pollution due to the absence or presence of nickel refineries is that of McNeely et al. (1972). They examined normal adults who were not occupationally exposed to nickel in Sudbury, Ontario, the location of North America's largest nickel refinery, and compared them to adults from Hartford, Connecticut. The Sudbury mean serum nickel level for 25 adults was 0.46 ± 0.14 with a range of 0.20 - .73 µg/dl, while respective values for Hartford were 0.26 ± 0.09 (range 0.08 - 0.52 µg/dl).

Data from two studies reporting values of nickel in blood for occupationally exposed persons and nonexposed controls show significant differences between these groups. Høgetveit and Barton (1976) reported on the results of monitoring blood plasma Ni levels in workers in the Falconbridge nickel refinery. They found Ni plasma values of 0.74 µg/dl for 701 samples

TABLE 7-1. "NORMAL" BLOOD NICKEL CONCENTRATIONS

Author	Method	Area	No. of Subjects	Serum(S) or Plasma (P)	Nickel concentration in μg/dl	
					Mean (± SD)	Range
Schaller et al. (1968)	Atomic absorption	Germany	26	P	2.1	0.6-3.7
Nomoto and Sunderman (1970)	Atomic absorption	Connecticut	40	S	0.26	0.11-0.46
McNeely et al. (1972)	Atomic absorption	Connecticut	26	S	0.26	0.08-0.52
Pekarek and Hauer (1972)	Atomic absorption	Washington, D.C.	20	S	1.5 (± 0.5)	-
Høgetveit and Barton (1976)	Atomic absorption	Norway	3	P	0.42	0.2-0.6
Spruit and Bongaarts (1977a)	Atomic absorption	Holland	10	P	0.16	-

from 305 workers while controls showed an average value of 0.42 μg/dl in 86 samples. Atomic absorption spectrometry was used in the analyses. The plasma levels for workers at different work stations showed that 179 electrolysis department workers had a mean blood nickel concentration of 0.74 μg/dl, while 126 roasting-smelting workers averaged 0.60 μg/dl. Workers engaged in electrolysis operations were found to be exposed to soluble nickel salts in aerosol form, while the workers in roasting-smelting operations were exposed to largely insoluble compounds in dust (Høgetveit and Barton, 1977).

Spruit and Bongaarts (1977a, 1977b) tested for blood plasma nickel levels in eight occupationally exposed volunteers and found average levels of 1.02 and 1.11 μg/dl at different periods during the work year, but 0.53 μg/dl after the annual two-week holiday. The controls, patients from the dermatology service without occupational exposure, showed plasma levels of 0.16 and 0.20 μg/dl for 10 males and 14 females, respectively. These data support the Høgetveit and Barton (1976) finding that plasma concentrations reflect current exposure and, further, provide evidence that there is very quick response to exposure.

The specific effects on blood levels of nickel from faulty hygiene and failure to observe safety regulations among exposed workers have either not been evaluated or, if evaluated, have not been reported.

Presented in Table 7-2 are urinary nickel levels measured in non-occupational groups in the United States and elsewhere. Mean levels in the various reports range from less than 1.0 to approximately 20 μg/liter, with more recent United States data conforming to the low end of the range.

In occupational settings, urinary levels are seen to be markedly elevated. Høgetveit and Barton (1976) found an average urine nickel concentration of 8.9 μg/dl for 729 samples from 305 workers, while the value for controls was 2.1 μg/dl. The data for average urine concentrations for different work sites and exposure to different nickel compounds were not given.

Spruit and Bongaarts (1977a, 1977b) found a mean nickel urine concentration of 1.8 μg/dl for seven occupationally exposed individuals and 0.06 μg/dl for 10 unexposed males. After a two-week vacation period, the mean value for the exposed workers had gone down to 0.18 μg/dl.

TABLE 7-2. NICKEL CONCENTRATIONS IN HUMAN URINE

Authors	Method	Area	No. of Subjects	Nickel concentration, μg/dl (μg/day) Mean	Nickel concentration, μg/dl (μg/day) Range
Sunderman (1965)	Atomic absorption	Pennsylvania	17	1.8 (19.8)	0.4-3.1
Nomoto and Sunderman (1970)	Atomic absorption	Connecticut	26	0.23 (2.4)	0.10-0.52 (1.0-5.6)
Lehnert et al. (1970)	Atomic absorption	Germany	15	(9.3)	(5.7-12.7)
McNeely et al. (1972)	Atomic absorption	Connecticut	20	0.20 (2.5)	0.07-0.40 (0.05-6.0)
Høgetveit and Barton (1976)	Atomic absorption	Norway	a	2.1	0.3-4.2
Spruit and Bongaarts (1977a,b)	Atomic absorption	Netherlands	10	0.06	a
Mikac-Devic et al. (1977)	Atomic absorption	Connecticut	a	0.27	a
Bernacki et al. (1978)	Atomic absorption	Connecticut	19	0.27[b]	0.04-0.51[b]
Ader and Stoeppler (1977)	Atomic absorption	a	a	0.2	a

[a] Not specified.

[b] Ni:2.5 ± 1.3 μg/g creatinine (range 0.7-5.7 μg/g creatinine); all samples with specific gravity < 1.012 discarded.

Bernacki et al. (1978) determined urine concentrations by volume and creatinine ratio for workers with different environmental exposures. Table 7-3 shows the findings for exposed, nonexposed, and control subjects, as well as air concentrations for seven work environments. There is only partial concordance between atmospheric concentrations and urine values.

Crucial to the assessment of the effects of nickel on human populations is the necessity of determining key tissue levels of the element and, where possible, total body burden. It is generally not feasible to assess these levels in humans other than through autopsy studies, and several investigators have carried out such surveys of nickel levels in selected organs. These studies can be roughly classed into case studies concerned with specific diseases or population studies, as discussed below. No _in vivo_ studies for nickel have been reported.

There are very few data in the literature concerning nickel tissue levels and total body burden. The National Academy of Sciences (1975) report summarized the available findings and concluded that the total nickel content in a normal man is approximately 10 mg.

Bernstein et al. (1974) reported results for 25 autopsies of subjects aged 20 to 40 years from New York City, with a diagnosis of sudden death and no indication of illness. Tissues were taken from the right lung and paratracheal, peribronchial, and hilar lymph nodes. Mean values were 0.23 ± 0.06 μg/Ni/g wet weight for lung tissue and 0.81 ± 0.41 for lymph nodes.

Sumino et al. (1975) reported various organ nickel levels taken from 30 Japanese subjects who died of varying causes. Mean values, expressed as μg/g wet weight, (and range) for lung, liver, and kidney were: 0.16 (0.04-0.44); 0.078 (0.028-0.22); and 0.098 (0.012-0.30), respectively.

Sunderman et al. (1971) found, in 4 subjects, the following mean (ppm, wet weight) levels of nickel for lung, liver and heart: 1.59, 0.87, and 0.61, respectively.

There is little in the literature reporting autopsy tissue studies of nickel refinery workers except from cases of fatal nickel carbonyl poisoning (Nickel. National Academy of Sciences, 1975), where highest levels of nickel are seen in lung, with lesser amounts in kidney, liver, and brain.

7.3.2 Effect and Dose-Response Relationships

The severity of a given marker effect is dependent upon the form and level of nickel exposure. In a number of experimental models of nickel

TABLE 7-3. NICKEL CONCENTRATIONS IN URINE SPECIMENS FROM WORKERS IN TWELVE OCCUPATIONAL GROUPS

Group	Occupation	No. of Subjects and sex	Description	Atmospheric Ni conc, µg/m^3[a]	Urine µg/ℓ.	Concn[a] µg/g creatinine
A	Hospital workers	19 (15M,4F)	Physicians, technologists, and clerks	Not measured	2.7±1.6 (0.4-5.1)	2.5±1.3 (0.7-5.7)
B	Nonexposed industrial workers	23 (20M,3F)	Managers, office workers and storekeepers	Not measured	3.2±2.6 (0.3-8.5)	2.7±1.7 (0.6-6.1)
C	Coal gasification workers	9M	Ni-catalyzed hydrogenation process workers	Not measured	4.2±2.4 (0.4-7.9)	3.2±1.6 (0.1-5.8)
D	Buffers/polishers	7 (6M,1F)	Abrasive buffing, polishing and deburring aircraft parts made of Ni alloys	26±48 (0.05-129)	4.1±3.2 (0.5-9.5)	2.4±1.4 (0.5-4.7)
E	External grinders	9 (7M,2F)	Abrasive wheel grinding of exteriors of parts made of Ni alloys	1.6±3.0 (2.1-8.8)	5.4±2.4 2.1-8.8)	3.5±1.6 1.7-6.1)
F	Arc welders	10 (7M,3F)	DC arc welding of aircraft parts made of Ni alloys	6.0±14.3 (0.2-46)	6.3±4.1[b] (1.6-14)	5.6±6.2 (1.1-17)
G	Bench mechanics	8 (4M,4F)	Assembling, fitting, and finishing parts made of Ni alloys	52±94 (0.01±252)	12.2±13.6[b] (1.4-41)	7.2±6.8[b] (0.7-20)
H	Nickel battery workers	6 (5M,1F)	Fabricating Ni-Cd or Ni-Zn electrical storage batteries	Not measured	11.7±7.75[c] (3.4-25)	10.2±6.4[c] (7.2-23)
I	Metal sprayers	5 (4M,1F)	Flame spraying Ni-containing powders in plasma phase onto aircraft parts	2.4±2.6 (0.04-6.5)	17.2±9.8[c] (1.4-26)	16.0±21.9 (1.4-54)
J	Electroplaters	11M	Intermittent exposure to Ni in combined electrodeposition operations involving Ag, Cd, Cr, or Cr plating as well as Ni	0.8±0.9 (0.04-2.1)	10.5±8.1[c] (1.3-30)	5.9±5.0[b] (1.0-20)
K	Nickel platers	21M	Full-time work in Ni plating operations	Not measured	27.5±21.2[d] (3.6-65)	19.0±14.7[d] (2.4-47)
L	Nickel refinery workers	15M	Workers in a nickel refinery that employs the electrolytic process	489±560 (20-2,200)	222±226[d] (8.6-8.3)	124±109[d] (6.1-287)

[a] Mean ± SD with range in parentheses.

[b] $p < 0.05$ vs control subjects in Group A, computed by t test.

[c] $p < 0.01$ vs control subjects in Group A, computed by t test.

[d] $p < 0.001$ vs control subjects in Group A, computed by t test.

Source: Bernacki (1978).

toxicity, a proportionality between the level of nickel and the severity of effect has been reported. In most cases, the levels of nickel administered were quite high and were administered parenterally to obtain maximum toxicological effect.

Similarly, the extensive literature dealing with the occupational carcinogenesis of nickel points to increased nasal and lung cancer risk with increasing levels of exposure to nickel in work place air.

Studies of accidental acute exposure of workmen to nickel carbonyl indicate that there is a gradient of serious injury depending on the amount of nickel carbonyl inhaled. According to Sunderman et al. (1971), an initial 8-hr. urine specimen having a nickel level less than 10 μg/dl is associated with mild exposure, and minimal symptomatology is apparent. Moderate exposure is associated with corresponding nickel levels of greater than 10 μg/dl but less than 50 μg/dl, while levels in excess of 50 μg/dl are associated with severe exposure resulting in serious illness and hospitalization.

With regard to the general population, the increased or persistent prevalence of nickel-related skin disorders generally reflects the widespread use of a variety of nickel-containing commodities. Given the clinical nature of nickel hypersensitivity and the route of exposure (external contact), it is difficult to place dose-response relationships in any kind of quantitative framework. Several studies suggest that there may exist a relationship between the flare-up of nickel dermatitis and the level of nickel in the diet. Well-designed epidemiological studies would be required to establish conclusive relationships between diet nickel and frequency of dermatitis occurrence.

In summary, then, it appears that the frequency or extent of various effects of nickel are generally related to the level or frequency of nickel exposure in man. A quantitative dose-response risk assessment is presented for cancer due to exposure to nickel in ambient air (Section 7.5.5).

7.4 POPULATIONS AT RISK

Populations at risk may be defined as those segments of the population who are placed at increased risk to the effects of nickel either by virtue of a special exposure status or by some physiological status that renders them more susceptible to nickel's effects. Thus, there are external and physiological aspects to the relationship of risk to nickel.

In terms of exposure, occupational groups, such as nickel workers and other workers engaged in handling nickel, obviously comprise the individuals at highest risk. With regard to the population at large, it appears that women, particularly housewives, are at special risk to nickel-induced skin disorders. In large part, this is due to the extended exposure to a number of nickel-containing commodities such as stainless-steel kitchens, jewelry and household chemicals. The dietary nickel-hypersensitivity relationship requires much further study.

With reference to heightened susceptibility to nickel effects by virtue of physiological status, the issue is far from clear. In Chapter 5 it was noted that a familial history of atopic dermatitis may predispose an individual to nickel hypersensitivity, but the difficulty in making clear distinctions between, or defining clear relationships of, nickel dermatitis and atopic dermatitis do not permit any firm conclusions to be drawn.

Although it remains to be clearly established, the role of nickel as a possible carcinogen or potentiator in the epidemiological association of cigarette smoking and respiratory cancer is suggestive; thus, cigarette smokers constitute a potential population at greater risk.

In Chapter 4 it was noted that nickel can cross the placental barrier in man and animals. Thus, one can classify women of child-bearing age as a potential risk population by virtue of risk to the conceptus in pregnancy. The paucity of data regarding *in utero* effects of low or moderate exposure to nickel in man limits any definition of the nature of fetal effects of nickel at the present time.

7.4.1 Numbers of the U.S. Population in Special Risk Categories

The epidemiological data on the prevalence of nickel hypersensitivity in the U.S. and elsewhere and as put forth in Chapter 5 do not permit the assessment of its true prevalence in the general population. Thus, one cannot determine numbers of individuals in the U.S. who fall into this category.

7.5 CURRENT REGULATIONS AND STANDARDS

7.5.1 Occupational Exposure

The threshold limit value (TLV) for nickel as a soluble inorganic salt is set at 0.1 mg/m^3 to prevent irritation (ACGIH, 1981). However, earlier TLV documentation states that this TLV is probably not sufficiently low to prevent dermatitis or sensitization from soluble salts and mists (ACGIH, 1976). The TLV for nickel carbonyl is set at .35 mg/m^3 (0.05 ppm) to prevent acute systemic effects (ACGIH, 1976; 1981).

The National Institute for Occupational Safety and Health (1977b) has recommended a standard of .007 mg/m^3 (0.001 ppm) for nickel carbonyl and that the compound be regulated as a carcinogen.

7.5.2 Dermal Exposure to Nickel in the Environment

The major problem posed by nickel for the United States population at large is nickel hypersensitivity, mainly via contact with many nickel-containing commodities. However, there are essentially no studies of general populations which quantitatively relate nickel exposure to the prevalence of nickel-related skin disorders such as contact dermatitis. Although an occupational TLV for nickel as a soluble inorganic salt has been set at 0.1 mg/m^3 to prevent irritation, no corresponding threshold value has been determined for nickel-sensitive individuals exposed to nickel in everyday contact with household commodities. At present, there is insufficient information to provide any quantitative guidelines for protecting sensitive individuals; avoidance of contact with nickel is the best obvious preventive measure.

7.5.3 Exposure to Nickel in Ambient Water

The U.S. Environmental Protection Agency (EPA, 1980) has recently set forth its criterion value for nickel in ambient water. Since ambient water levels are of more significance for the general United States population than TLV values directed to occupational settings, the former will be discussed.

In arriving at an oral criterion for nickel, several factors were taken into account. There is little evidence for accumulation of nickel in various tissues. Absorption through the gastrointestinal tract is low. Acute exposure of man to nickel, particularly nickel carbonyl, is primarily of concern in workplaces. In many of these situations, inhalation is the main route of entry and the lung is the critical organ. Although certain nickel compounds have been shown to be carcinogenic in humans and experimental animals, there is no evidence for carcinogenicity due to the presence of nickel in the diet. The role of nickel as an essential element is a confounding factor in any risk estimate.

In order to develop an oral risk assessment based on toxicological effects other than carcinogenicity, dose-response data would have been most helpful. However, while the frequency or extent of various effects of nickel are related to the level or frequency of nickel exposure in man, the relevant data do not permit any quantitative estimation for oral dose-response relationships. Studies published in the available literature have not demonstrated a no-observable-effect level (NOEL); therefore, the study demonstrating the lowest-observable-adverse-effect level (LOAEL) was used in establishing a criterion level for nickel in drinking water.

The study originally used as a basis for a risk estimate was that of Schroeder and Mitchner (1971) in which adverse effects in rats were demonstrated at a level of 5 mg/ℓ (5 ppm) in drinking water. However, since the publication of the ambient water quality criterion (Environmental Protection Agency, 1980), several limitations regarding the Schroeder and Mitchner (1971) study have surfaced which preclude its use as a basis for a risk estimate. These include: (1) suggestive inappropriate randomization of experimental animals in their cages, (2) lack of historical data for control animals, and (3) failure of subsequent studies to support the effects noted at 5 ppm.

Examination of other studies for possible use in calculating an oral risk estimate reveals that effects in test animals due to nickel challenge have been reported within a range of 250-1000 ppm nickel administered via diet (Ling and Leach, 1979; Ambrose et al., 1976; O'Dell et al., 1970; Weber and Reid, 1968; Phatak and Patwardhan, 1950). The reported effects have primarily been those of depressed body weight and growth in the test animals. A number of problems beset these studies in regard to their usefulness for calculating a risk estimate: i.e., use of non-mammalian test animals (Ling and Leach, 1979; Weber and Reid, 1968); use of semi-purified diets (Weber and Reid, 1968); lack of paired feeding controls (Ling and Leach, 1979; Ambrose et al., 1976; O'Dell et al., 1970); nevertheless, collectively, the studies suggest that nickel may induce adverse effects within the range of 250-1000 ppm. In the Phatak and Patwardhan study (1950), statistical analysis (statistical tests not reported) showed no effect differences between control and treated rats; however, this same study did show transplacental passage of nickel up to 22-30 ppm when dams received 1000 ppm Ni in their diet.

Of particular interest is the study of Ambrose et al. (1976) where, in a multigeneration study in rats, the authors reported a higher incidence of stillbirths in the first generation of rats fed dietary concentrations of nickel of 0, 250, 500, and 1,000 ppm. Although the authors did not report performing any statistical tests on these data, the effect of higher stillbirth incidence, coupled with teratogenic effects reported in several animal species (albeit routes of exposure other than oral) (Gilani and Marano, 1980; Sunderman et al., 1980b, 1979a; Lu et al., 1979; Ferm, 1972) are such that the data have been deemed worth further analysis. However, as noted previously, this study imposes not only interpretive problems, but statistical problems as well relating to the independence of stillbirths within a litter. These problems, as well as other issues relevant to determining an oral criterion, are discussed in greater detail elsewhere (Seilkop, 1982; Sivulka, 1982). A human health water quality criterion of 632 µg/ℓ based upon the Ambrose et al. study has been derived.

7.5.4 Exposure to Nickel in Ambient Air

There are presently no standards set based upon exposure to nickel in ambient air. This is due, in part, to the fact that inhalation, as a route of exposure, has been historically considered as less relevant, in terms of magnitude, to the general U.S. population than have other routes of exposure. The amounts of ambient air nickel entering the respiratory tract are quite small, an average of less than 1 µg in nonsmokers to 3-15 µg/day for a 2 pack/day cigarette smoker, as compared to an average daily ingestion of nickel on the order of 300 to 600 µg. This absence of a standard is also due, in part, to the perception of nickel as an agent of lower toxicological potential than other elements such as lead, cadmium and mercury. This perception may be warranted in terms of the noncarcinogenic, low-level effects of nickel, but is questionable in terms of nickel's carcinogenic potential.

7.6 QUANTITATIVE ESTIMATION OF CANCER RISK FOR NICKEL

7.6.1 Introduction

There is no question, based upon studies of workers in nickel refineries, that nickel in some form(s) is carcinogenic to man by the inhalation route. Therefore, a case can be made for deriving an air quality criterion based upon carcinogenic effects. Such a derivation is presented below, albeit recognizing that some of the forms of nickel in the ambient air may not be carcinogenic.

This quantitative section deals with the unit risk for nickel in air and the potency of nickel relative to other carcinogens that the U.S. Environmental Protection Agency Carcinogen Assessment Group (CAG) has evaluated. The unit risk estimate for an air pollutant is defined as the lifetime cancer risk occurring in a hypothetical population in which all individuals are exposed continuously from birth throughout their lifetimes to a concentration of 1 $\mu g/m^3$ of the agent in the air which they breathe. This calculation is done to estimate in quantitative terms the impact of the agent as a carcinogen. Unit risk estimates are used for two purposes: 1) to compare the carcinogenic potency of several agents with each other, and 2) to give a crude indication of the population risk which might be associated with air or water exposure to these agents, if the actual exposures are known.

7.6.2 Procedures for Determination of Unit Risk from Animal Data

The data used for the quantitative estimate is one or both of two types: 1) lifetime animal studies, and 2) human studies where excess cancer risk has been associated with exposure to the agent. In animal studies it is assumed, unless evidence exists to the contrary, that if a carcinogenic response occurs at the dose levels used in the study, then responses will also occur at all lower doses with an incidence determined by the extrapolation model.

There is no solid scientific basis for any mathematical extrapolation model that relates carcinogen exposure to cancer risks at the extremely low concentrations that must be dealt with in evaluating environmental hazards. For practical reasons, such low levels of risk cannot be measured directly either by animal experiments or by epidemiologic studies. We must, therefore, depend on our current understanding of the mechanisms of carcinogens for guidance as to which risk model to use. At the present time the dominant view of the carcinogenic process involves the concept that most agents that cause cancer also cause irreversible damage to DNA. This position is reflected by the fact that a very large proportion of agents that cause cancer are also mutagenic. There is reason to expect the quantal type of biological response that is characteristic of mutagenesis is associated with a linear non-threshold dose-response relationship. Indeed, there is substantial evidence from mutagenicity studies with both ionizing radiation and a wide variety of chemicals that this type of dose-response model is the appropriate one to use. This is particularly true at the lower end of the dose-response curve; at higher doses, there can be an upward curvature probably reflecting the effects of multistage processes on the mutagenic response. The linear non-threshold dose-response relationship is also consistent with the relatively few epidemiologic studies of cancer responses to specific agents that contain enough information to make the evaluation possible (e.g., radiation-induced leukemia, breast and thyroid cancer, skin cancer induced by arsenic in drinking water, liver cancer induced by aflatoxin in the diet). There is also some evidence from animal experiments that is consistent with the linear non-threshold model (e.g., liver tumors induced in mice by 2-acetylaminofluorene in the large scale ED_{01} study at the National Center for Toxicological Research and the initiation stage of the two-stage carcinogenesis model in rat liver and mouse skin).

Because it has the best, albeit limited, scientific basis of any of the current mathematical extrapolation models, the linear non-threshold model has been adopted as the primary basis for animal-to-human risk extrapolation to low levels of the dose-response relationship. The risk estimates made with this model should be regarded as conservative, representing the most plausible upper-limit for the risk, i.e., the true risk is not likely to be higher than the estimate, but it could be lower.

The mathematical formulation chosen to describe the linear non-threshold dose-response relationship at low doses is the linearized multistage model. This model employs enough arbitrary constants to be able to fit almost any monotonically increasing dose-response data and it incorporates a procedure for estimating the largest possible linear slope (in the 95% confidence limit sense) at low extrapolated doses that is consistent with the data at all dose levels of the experiment.

7.6.2.1 Description of the Low Dose Animal-to-Human Extrapolation Model--Let P(d) represent the lifetime risk (probability) of cancer at dose d. The multistage model has the form

$$P(d) = 1 - \exp\,[-(q_0 + q_1d + q_2d^2 + \ldots + q_kd^k)]$$

where

$$q_i \geq 0,\ i = 0, 1, 2, \ldots, k$$

Equivalently,

$$P_t(d) = 1 - \exp\ [(q_1 d + q_2 d^2 + \ldots + q_k d^k)]$$

where

$$P_t(d) = \frac{P(d) - P(o)}{1 - P(o)}$$

is the extra risk over background rate at dose d, or the effect of treatment.

The point estimate of the coefficients q_i, $i = 0, 1, 2, \ldots, k$, and consequently the extra risk function $P_t(d)$ at any given dose d, is calculated by maximizing the likelihood function of the data.

The point estimate and the 95% upper confidence limit of the extra risk $P_t(d)$ are calculated by using the computer program GLOBAL 79 developed by Crump and Watson (1979). At low doses, upper 95% confidence limits on the extra risk and lower 95% confidence limits on the dose producing a given risk are determined from a 95% upper confidence limit, q_1^*, on parameter q_1. Whenever $q_1 > 0$, at low doses the extra risk A(d) has approximately the form $A(d) = q_1 \times d$. Therefore, $q_1 \times d$ is a 95% upper confidence limit on the extra risk and R/q_1^* is a 95% lower confidence limit on the dose producing an extra risk of R. Let L_0 be the maximum value of the low-likelihood function. The upper limit q_1 is calculated by increasing q_1 to a value q_1^* such that when the log-likelihood is remaximized subject to this fixed value q_1^* for the linear coefficient, the resulting maximum value of the log-likelihood L_1 satisfies the equation

$$2\ (L_0 - L_1) = 2.70554$$

where 2.70554 is the cumulative 90% point of the chi-square distribution with one degree of freedom, which corresponds to a 95% upper-limit (one-sided). This approach of computing the upper confidence limit for the extra risk A(d) is an improvement on the Crump et al. (1977) model. The upper confidence limit for the extra risk calculated at low doses is always linear. This is conceptually consistent with the linear non-threshold concept discussed earlier. The slope, q_1^*, is taken as an upper bound of the potency of the chemical in inducing cancer at low doses. (In the section calculating the risk estimates, $P_t(d)$ will be abbreviated as P).

In fitting the dose-response model, the number of terms in the polynomial is chosen equal to (h-1), where h is the number of dose groups in the experiment including the control group.

Whenever the multistage model does not fit the data sufficiently well, data at the highest dose is deleted and the model is refitted to the rest of the data. This is continued until an acceptable fit to the data is obtained. To determine whether or not a fit is acceptable, the chi-square statistic

$$X^2 = \sum_{i=1}^{h} \frac{(X_i - N_iP_i)^2}{N_iP_i\ (1-P_i)}$$

is calculated where N_i is the number of animals in the i^{th} dose group, X_i is the number of animals in the i^{th} dose group with a tumor response, P_i is the probability of a response in the i^{th} dose group estimated by fitting the multistage model to the data, and h is the number of remaining groups. The fit is determined to be unacceptable whenever X^2 is larger than the cumulative 99% point of the chi-square distribution with f degrees of freedom, where f equals the number of dose groups minus the number of non-zero multistage coefficients.

7.6.2.2 Selection of Animal Data--For some chemicals, several studies in different animal species, strains, and sexes, each run at several doses and different routes of exposure are available. A choice must be made as to which of the data sets from several studies to use in the model. It may also be appropriate to correct for metabolism differences between species and absorption factors via different routes of administration. The procedures used in evaluating these data are consistent with the approach of making a maximum-likely risk estimate. Tney are listed below.

1. The tumor incidence data are separated according to organ sites or tumor types. The set of data (i.e., dose and tumor incidence) used in the model is the set where the incidence is statistically significantly higher than the control for at least one test dose level and/or where the tumor incidence rate shows a statistically significant trend with respect to dose level. The data set which gives the highest estimate of the lifetime carcinogenic risk, q_1^*, is selected in most cases. However, efforts are made to exclude data sets which produce spuriously high risk estimates because of a small number of animals. That is, if two sets of data show a similar dose-response relationship, and one has a very small sample size,

the set of data which has larger sample size is selected for calculating the carcinogenic potency.

2. If there are two or more data sets of comparable size which are identical with respect to species, strain, sex, and tumor sites, the geometric mean of q_1^*, estimated from each of these data sets, is used for risk assessment. The geometric mean of numbers $A_1, A_2, \ldots, A_m$ is defined as

$$(A_1 \times A_2 \times \ldots \times A_m)^{1/m}$$

3. If two or more significant tumor sites are observed in the same study, and if the data are available, the number of animals with at least one of the specific tumor sites under consideration is used as incidence data in the model.

7.6.2.3 Calculation of Human Equivalent Dosages from Animal Data--Following the suggestion of Mantel and Schneiderman (1977), we assume that mg/surface area/day is an equivalent dose between species. Since, to a close approximation, the surface area is proportional to the 2/3rds power of the weight as would be the case for a perfect sphere, the exposure in mg/day per 2/3rds power of the weight is also considered to be equivalent exposure. In an animal experiment this equivalent dose is computed in the following manner. Let

L_e = duration of experiment
l_e = duration of exposure
m = average dose per day in mg during administration of the agent (i.e., during l_e), and
W = average weight of the experimental animal

Then, the lifetime average exposure is

$$d = \frac{l_e \times m}{L_e \times W^{2/3}}$$

7.6.2.3.1 Oral exposure. Often exposures are not given in units of mg/day and it becomes necessary to convert the given exposures into mg/day. For example, in most feeding studies exposure is in terms of ppm in the diet. Similarly, in drinking water studies, exposure is in ppm in the water. In these cases the exposure in mg/day is

$$m = \text{ppm} \times F \times r$$

where ppm is parts per million of the carcinogenic agent in the diet or water, F is the weight of the food or water consumed per day in kg, and r is the absorption fraction. In the absence of any data to the contrary, r is assumed to be equal to one. For a uniform diet, the weight of the food consumed is proportional to the calories required, which in turn is proportional to the surface area or 2/3rds power of the weight. Water demands are also assumed proportional to the surface area, so that

$$m \propto ppm \times W^{2/3} \times r$$

or

$$\frac{m}{rW^{2/3}} \propto ppm$$

As a result, ppm in the diet or water is often assumed to be an equivalent exposure between species. However, we feel that this is not justified since the calories/kg of food is very different in the diet of man compared to laboratory animals primarily due to moisture content differences. Consequently, the amount of drinking water required by each species also differs because of the amount of moisture in the food. Therefore, we use an empirically-derived factor, f = F/W, which is the fraction of a species body weight that is consumed per day as food or water. We use the following rates:

Species	W	f food	f water
Man	70	0.028	0.029
Rats	0.35	0.05	0.078
Mice	0.03	0.13	0.17

Thus, when the exposure is given as a certain dietary or water concentration in ppm, the exposure in mg/$W^{2/3}$ is

$$\frac{m}{rW^{2/3}} \propto \frac{ppm \times F}{W^{2/3}} = \frac{ppm \times f \times W}{W^{2/3}} = ppm \times f \times W^{1/3}$$

When exposure is given in terms of mg/kg/day = m/Wr = s, the conversion is simply

$$\frac{m}{rW^{2/3}} = s \times W^{1/3}$$

7.6.2.3.2 Inhalation exposure. When exposure is via inhalation, the calculation of dose can be considered for two cases where 1) the carcinogenic agent is either a completely water-soluble gas or an aerosol, and is absorbed proportionally to the amount of air breathed in, and 2) where the carcinogen is a poorly water-soluble gas which reaches an equilibrium between the air breathed and the body compartments. After equilibrium is reached, the rate of absorption of these agents is expected to be proportional to the metabolic rate, which in turn is proportional to the rate of oxygen consumption, which in turn is a function of surface area.

Case 1--

Agents that are in the form of particulate matter or virtually completely absorbed gases, such as SO_2, can reasonably be expected to be absorbed proportional to the breathing rate. In this case the exposure in mg/day may be expressed as

$$m = I \times v \times r$$

where I = inhalation rate per day in m^3, v = mg/m^3 of the agent in air, and r = the absorption fraction.

The inhalation rates, I, for various species can be calculated from the observations (Federation of American Societies for Experiemental Biology, 1974) that 25 g mice breathe 34.5 liters/day and 113 g rats breathe 105 liters/day. For mice and rats of other weights, W (in kilograms), the surface area proportionality can be used to find breathing rates in m^3/day as follows:

$$\text{For mice, } I = 0.0345\ (W/0.025)^{2/3}\ m^3/\text{day}$$
$$\text{For rats, } I = 0.105\ (W/0.113)^{2/3}\ m^3/\text{day}$$

For humans, the value of 20 m^3/day* is adopted as a standard breathing rate (ICRP 1977).

The equivalent exposure in $mg/W^{2/3}$ for these agents can be derived from the air intake data in a way analogous to the food intake data. The empirical factors for the air intake per kg per day, i = I/W, based upon the previous stated relationships are tabulated as follows:

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*From "Recommendation of the International Commission on Radiological Protection", page 9. The average breathing rate is 10^7 cm^3 per 8-hour workday and 2×10^7 cm^3 in 24 hours.

Species	W	i = I/W
Man	70	0.29
Rats	0.35	0.64
Mice	0.03	1.3

Therefore, for particulates or completely absorbed gases, the equivalent exposure in mg/$W^{2/3}$ is

$$d = \frac{m}{W^{2/3}} = \frac{Ivr}{W^{2/3}} = \frac{iWvr}{W^{2/3}} = iW^{1/3}vr$$

In the absence of experimental information or a sound theoretical argument to the contrary, the fraction absorbed, r, is assumed to be the same for all species.

Case 2--

The dose in mg/day of partially soluble vapors is proportional to the O_2 consumption, which in turn is proportional to $W^{2/3}$ and is also proportional to the solubility of the gas in body fluids, which can be expressed as an absorption coefficient, r, for the gas. Therefore, expressing the O_2 consumption as $O_2 = k\, W^{2/3}$, where k is a constant independent of species, it follows that

$$m = k\, W^{2/3} \times v \times r$$

or

$$d = \frac{m}{W^{2/3}} = kvr$$

As with Case 1, in the absence of experimental information or a sound theoretical argument to the contrary, the absorption fraction, r, is assumed to be the same for all species. Therefore, for these substances a certain concentration in ppm or μg/m^3 in experimental animals is equivalent to the same concentration in humans. This is supported by the observation that the minimum alveolar concentration necessary to produce a given "stage" of anesthesia is similar in man and animals (Dripps et al., 1977). When the animals are exposed via the oral route and human exposure is via inhalation or vice-versa, the assumption is made, unless there is pharmacokinetic evidence to the contrary, that absorption is equal by either exposure route.

7.6.2.3.3 Adjustment of dose for less than lifespan duration of experiment. If the duration of experiment (L_e) is less than the natural life-span of the test animal (L), the slope q_1^*, or more generally the exponent g(d), is increased by multiplying a factor $(L/L_e)^3$. We assume that if the average dose d, is continued, the age-specific rate of cancer will continue to increase as a constant function of the background rate. The age-specific rates for humans increase at least by the 2nd power of the age and often by a considerably higher power as demonstrated by Doll (1971). Thus, we would expect the cumulative tumor rate to increase by at least the 3rd power of age. Using this fact, we assume that the slope q_1^*, or more generally the exponent g(d), would also increase by at least the 3rd power of age. As a result, if the slope q_1^* [or g(d)] is calculated at age L_e, we would expect that if the experiment had been continued for the full lifespan, L, at the given average exposure, the slope q_1^* [or g(d)] would have been increased by at least $(L/L_e)^3$.

This adjustment is conceptually consistent with the proportional hazard model proposed by Cox (1972) and the time-to-tumor model considered by Crump (1979) where the probability of cancer by age t and at dose d is given by

$$P(d,t) = 1 - \exp [-f(t) \times g(d)]$$

7.6.2.4 Calculation of the Unit Risk--The 95% upper limit risk associated with d mg/kg$^{2/3}$/day is obtained from GLOBAL 79 and, for most cases of interest to risk assessment, can be adequately approximated by $P(d) = 1 - \exp(-q_1^* d)$. A "unit risk" in units X is simply the risk corresponding to an exposure of X = 1. To estimate this value we simply find the number of mg/kg$^{2/3}$/day corresponding to one unit of X and substitute this value into the above relationship. Thus, for example, if X is in units of μg/m^3 in the air, we have that for case (1) $d = 0.29 \times 70^{1/3} \times 10^{-3}$ mg/kg$^{2/3}$/day and for case (2) d = 1, when μg/m^3 is the unit used to compute parameters in animal experiments.

If exposures are given in terms of ppm in air, we may simply use the fact that

$$1 \text{ ppm} = 1.2 \times \frac{\text{molecular weight (gas)}}{\text{molecular weight (air)}} \text{ mg/m}^3$$

Note, an equivalent method of calculating unit risk would be to use mg/kg for the animal exposures and then increase the jth polynomial coefficient by an amount

$$(W_h/W_a)^{j/3} \quad j = 1, 2, \ldots, k$$

and use mg/kg equivalents for the unit risk values.

7.6.2.5 Interpretation of Quantitative Estimates--For several reasons, the unit risk estimate is only an approximate indication of the absolute risk in populations exposed to known carcinogen concentrations. First, there are important species differences in uptake, metabolism, and organ distribution of carcinogens, as well as species differences in target site susceptibility, immunological responses, hormone function, dietary factors, and disease. Second, the concept of equivalent doses for humans compared to animals on a mg/surface area basis is virtually without experimental verification regarding carcinogenic response. Finally, human populations are variable with respect to genetic constitution and diet, living environment, activity patterns, and other cultural factors.

The unit risk estimate can give a rough indication of the relative potency of a given agent compared with other carcinogens. The comparative potency of different agents is more reliable when the comparison is based on studies in the same test species, strain, and sex, and by the same route of exposure, preferably by inhalation.

The quantitative aspect of the carcinogen risk assessment is included here because it may be of use in the regulatory decision-making process, e.g., setting regulatory priorities, evaluating the adequacy of technology-based controls, etc. However, it should be recognized that the estimation of cancer risks to humans at low levels of exposure is uncertain. At best, the linear extrapolation model used here provides a rough, but plausible estimate of the upper-limit of risk; i.e., it is not likely that the true risk would be much more than the estimated risk, but it could very well be considerably lower. The risk estimates presented in subsequent sections should not be regarded as an accurate representation of the true cancer risks even when the exposures are accurately defined. The estimates presented may be factored into regulatory decisions to the extent that the concept of upper risk limits is found to be useful.

7.6.2.6 Alternative Methodological Approaches--The methods used by the CAG for quantitative assessment are consistently conservative, i.e., tending toward high estimates of risk. The most important part of the methodology contributing to this conservatism in this respect is the linear non-threshold extrapolation model. There are a variety of other extrapolation models that could be used, most of which would give lower risk estimates. In other documents, other models have been used for comparative purposes only. However, the animal data for nickel have only two dosages; these limited data do not allow estimation of the parameters necessary for fitting these other models.

The position is taken by the CAG that the risk estimates obtained by use of the linear non-threshold model are upper-limits and the true risk could be lower.

With respect to the choice of animal bioassay as the basis for extrapolation, the present approach is to use the most sensitive responder. Alternatively, the average responses of all the adequately tested bioassays could be used.

7.6.3 Cancer Risk Unit Estimates Based on Animal Studies

An extensive animal data base indicates that many nickel compounds induce cancer either by injection or inhalation (National Institute of Occupational Safety and Health 1977a; IARC 1976, 1973). Some studies have suggested that the ability of nickel compounds to induce tumors following parenteral administration is related to their aqueous solubility (Sunderman and Maenza, 1976; Sunderman, 1973; Payne 1965, 1964), although one recent study found essentially no correlation between solubility and injection site tumors (Sunderman, 1981).

Table 7-4 summarizes the results of five chronic inhalation experiments on nickel compounds, four of which showed that nickel was carcinogenic. Only one of these four (Ottolenghi 1974) can be used for a quantitative risk assessment.

A risk assessment cannot be made from the experiment of Sunderman and co-workers (1959, 1957), because survival was too poor. Only 9 of 96 (9 percent) exposed animals survived for two years. The toxicity can be attributed to the administration of nickel carbonyl in an alcohol-ether mixture, evidenced by the fact that only 3/41 (7 percent) of the vehicle control rats survived two years. In a subsequent experiment (Sunderman and Donnelly 1965), only one of 64 rats chronically exposed to nickel carbonyl developed a lung tumor. In rats acutely exposed, two lung tumors were

TABLE 7-4. INHALATION EXPERIMENTS WITH NICKEL COMPOUNDS

Author and Year	Species	Form of Nickel	Treatment Dose	No. of Animals	Duration	Significant Findings
Sunderman et al. 1957, 1959	Male albino Wistar rats	Nickel Carbonyl	1. 0.03 mg per liter for 30 minutes 3 times weekly 2. 0.06 mg per liter for 30 minutes 3 times weekly 3. Controls (received only ether-alcohol mixture)	1. 64 2. 32 3. 41	52 weeks 52 weeks 52 weeks	4/9 rats surviving 2 yrs developed neoplasms of the lung. 0/3 surviving controls developed neoplasms of the lung.
Ottolenghi et al. 1974	Pathogen-free male and female F344 rats	Nickel sulfide (Ni_3S_2)	1. 0.97 mg/m^3 5 days/week 6 hours/day 2. Controls (received clean air)	1. 208 2. 215	78 weeks (observed for additional 30 week period)	Exposed: 29/208 had lung tumors. Controls: 2/215 had lung tumors.
Hueper 1958	1. Guinea pigs of inbred strain 13 2. Wistar rats 3. Bethesda black rats 4. C57 black mice	Nickel powder	15 mg/m^3 6 hours/day 4-5 days/week	1. 42 2. 100 3. 160 4. 20	Maximal period of 21 months (until death)	In guinea pigs and rats, "abnormal multicentric adenomatoid formation" in lung. In mice, 2 lymphosarcomas.

TABLE 7-4. (continued)

Author and Year	Species	Form of Nickel	Treatment Dose	No. of Animals	Duration	Significant Findings
Wehner et al. 1975	Syrian Golden hamsters	NiO	1. 53.2 μg/ℓ (average) 7 hours/day, 5 days/week	1. 51	25 months	NiO did not appear to increase incidence of lung tumors. However, two osteosarcomas and one rhabdosarcoma were observed in NiO exposed groups.
			2. Same as (1) plus cigarette smoke	2. 51		
			3. Cigarette smoke plus sham dust	3. 51		
			4. Sham, cigarette smoke, and sham dust	4. 51		
Sunderman and Donnelly 1965	Wistar male white rats	Nickel carbonyl	1. 80 ppm (0.6 mg/ℓ) for 30 minutes	1. 285	Single exposure (& Lifetime Observ.)	In 71 surviving rats 9 malignant lymphomas 1 lung adenocarcinoma 6 tumors at other sites.
			2. Same as (1) plus Dithiocarb*	2. 60	Single exposure (& Lifetime Observ.)	8 malignant lymphomas 1 lung tumor (anaplastic) 8 tumors at other sites.
			3. Alcohol-ether mixture for 30 minutes	3. 19	Single exposure (& Lifetime Observ.)	3 malignant lymphomas 2 tumors at other sites.
			4. Alcohol-ether mixture plus Dithiocarb*	4. 19	Single exposure (& Lifetime Observ.)	4 malignant lymphomas 2 tumors at other sites.

TABLE 7-4. (continued)

Author and Year	Species	Form of Nickel	Treatment Dose	No. of Animals	Duration	Significant Findings
Sunderman and Donnelly 1965	Wistar male white rats	Nickel carbonyl	5. 4 ppm (0.03 mg/ℓ) for 30 minutes 3 times weekly	5. 64	Duration of lifetime	5 malignant lymphomas 1 lung adenocarcinoma 1 tumor at other site.
			6. Alcohol-ether mixture only for 30 minutes 3 times weekly	6. 32	Duration of lifetime	1 malignant lymphoma 4 tumors at other sites.

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* Dithiocarb was administered subcutaneously. It is a treatment which in humans is efficacious in treating acute nickel carbonyl poisoning.

observed. Because the acute and chronically exposed groups cannot be combined, the number of lung tumors observed was too small for a risk assessment to be made from this data. A high incidence of malignant lymphomas was also observed in this experiment. The authors concluded that a relationship to nickel exposure appeared doubtful in view of a high spontaneous incidence of lymphoma in rats reported in the literature and found among control animals. A risk assessment cannot be made from Hueper's (1958) data because no control groups were used. Wehner et al. (1975) concluded that nickel oxide did not appear to cause lung tumors under his experimental conditions.

In the Ottolenghi et al. study (1974), 110 male and 98 female Fischer 344 rats were exposed to 970 μg/m^3 nickel sulfide inhalations for 78 weeks (5 days/wk, 6 hrs/day). Compared with 108 male and 107 female controls, the treated groups of both sexes showed statistically significant increases in both adenomas and adenocarcinomas of the lung. These results are shown in Table 7-5.

The results show significant increases in adenomas and in combined adenomas/adenocarcinomas for both males and females and also an increased incidence of squamous cell carcinoma of the lung in treated males and females. Since the authors conclude that these "benign and malignant neoplasms....are but stages of development of a single proliferative lesion" a unit risk assessment can be calculated which includes combined adenomas and adenocarcinomas.

Based on combining adenomas and adenocarcinomas and adding in squamous cell carcinomas, the treated males had a 14.5 percent incidence (16/110) versus 1 percent (1/108) for the controls. The equivalent lifetime continuous exposure is:

$$970\ \mu g/m^3 \times \frac{6}{24}\ \text{hrs} \times \frac{5}{7}\ \text{day} \times \frac{78}{110}\ \text{wks} = 122.8\ \mu g/m^3$$

Since nickel sulfide is a particulate, the equivalent human dosage is estimated according to Case 1, Section 7.6.2.3.2, where

$$d = iW^{1/3}vr$$

where d = equivalent exposure in mg/W$^{2/3}$, i for rats = .64, i for humans = .29, v = mg/m^3 of nickel sulfide in air, and r, the absorption fraction, is assumed equal in both species. Setting d equal in both species gives

$$v_{humans} = (i_{rats}/i_{humans})(W_{rats}/W_{humans})^{1/3}v_{rats}$$

TABLE 7-5. HYPERPLASTIC AND NEOPLASTIC CHANGES IN LUNGS OF RATS EXPOSED TO NICKEL SULFIDE

Pathologic Changes	Controls Males (108[a])	Controls Females (107[a])	Nickel Sulfide Males (110[a])	Nickel Sulfide Females (98[a])	P values Males	P values Females
Typical hyperplasia	26[b] (24)	20 (19)	68 (62)	65 (66)		
Atypical hyperplasia	17 (16)	11 (10)	58 (53)	48 (49)		
Squamous metaplasia	6 (6)	4 (4)	20 (18)	18 (18)		
Tumors:						
Adenoma	0 (0)	1 (1)	8 (7)	7 (7)	.005	.02
Adenocarcinoma	1 (1)	0 (0)	6 (5)	4 (4)	.06	.05
Squamous cell carcinoma	0 (0)	0 (0)	2 (2)	1 (1)		
Fibrosarcoma	0 (0)	0 (0)	1 (1)	0 (0)		

[a] Number of animals.

[b] Values represent the number of affected animals in each group. Percentage of affected animals is given in parentheses. Subtreatment groups were combined, since no significant differences were found among them.

Source: Ottolenghi et al. (1974).

Filling in the numbers gives

$$v_h = (.64/.29)(.35/70)^{1/3}\ 122.8\ \mu g/m^3 = 46.3\ \mu g/m^3$$

Use of the multistage model with the above data results in an upper limit risk estimate of the linear component of $q_1^* = 4.8 \times 10^{-3} (\mu g/m^3)^{-1}$.

Thus, based on animal studies, the upper limit risk to humans breathing 1 μg nickel sulfide/m^3 over a lifetime is 4.8×10^{-3}. If only the nickel content of the compounds had been considered, adjusting for the 73 percent weight composition of nickel, the upper-limit estimate would have been 6.6×10^{-3}.

7.6.4 Model for estimation of Unit Risk Based on Human Data

If human epidemiologic studies and sufficiently valid exposure information are available for the compound, they are always used in some way. If they show a carcinogenic effect, the data are analyzed to give an estimate of the linear dependence of cancer rates on lifetime average dose, which is equivalent to the factor B_H. If they show no carcinogenic effect when positive animal evidence is available, then it is assumed that a risk does exist, but it is smaller than could have been observed in the epidemiologic study, and an upper-limit to the cancer incidence is calculated assuming hypothetically that the true incidence is just below the level of detection in the cohort studied, which is determined largely by the cohort size. Whenever possible, human data are used in preference to animal bioassay data.

Very little information exists that can be utilized to extrapolate from high exposure occupational studies to low environmental levels. However, if a number of simplifying assumptions are made, it is possible to construct a crude dose-response model whose parameters can be estimated using vital statistics, epidemiologic studies, and estimates of worker exposures.

In human studies, the response is measured in terms of the relative risk of the exposed cohort of individuals compared to the control group. The mathematical model employed assumes that for low exposures the lifetime probability of death from lung cancer (or any cancer), P_0, may be represented by the linear equation

$$P_0 = A + B_H x$$

where A is the lifetime probability in the absence of the agent, and x is the average lifetime exposure to environmental levels in some units, say ppm. The factor, B_H, is the increased probability of cancer associated with each unit increase of the agent in air.

If we make the assumption that R, the relative risk of lung cancer for exposed workers, compared to the general population, is independent of the length or age of exposure but depends only upon the average lifetime exposure, it follows that

$$R = \frac{P}{P_0} = \frac{A + B_H (x_1 + x_2)}{A + B_H (x_1)}$$

or

$$RP_0 = A + B_H (x_1 + x_2)$$

where x_1 = lifetime average daily exposure to the agent for the general population, x_2 = lifetime average daily exposure to the agent in the occupational setting, and P_0 = lifetime probability of dying of cancer with no or negligible agent exposure.

Substituting $P_0 = A + B_H x_1$ and rearranging gives

$$B_H = P_0 (R - 1)/x_2$$

To use this model, estimates of R and x_2 must be obtained from the epidemiologic studies. The value P_0 is derived from the age-cause-specific death rates for combined males found in 1976 U.S. Vital Statistics tables using the life table methodology. For lung cancer the estimate of P_0 is 0.036. This methodology is used in the section on unit risk based on human studies.

7.6.5 Cancer Risk Estimates Based on Human Studies

The epidemiological/occupational studies discussed in the cancer epidemiology section show increases in both nasal and lung cancer. Exposures at the various plants, however, and at various locations within the plant were to several different compounds of nickel. Exposures at the Port Colborne, Ontario plant, included exposures to nickel subsulfide and nickel oxide in the high temperature, calcining and sinter furnace areas. Fifty-five of the 90 workers who developed lung cancer had been employed in one of these areas for at least one year. Furthermore, 21 of the 35 remaining workers who developed lung cancers were exposed to nickel from electrolysis operations associated with exposures to nickel sulfate, nickel chloride, nickel metal and nickel carbonate (National Institute of Occupational Safety and Health, 1977a). In the Clydach, Wales plant, high nickel dust and fume concentrations were present in the calciner buildings prior to 1925; after 1925 more moderate exposures were predominant. In the Kristiansand, Norway plant, concentrations of nickel chloride and nickel sulfate were measured. In all three of these plants exposures to different forms and concentrations of nickel varied by area.

Although a general weakness exists in attempting a unit risk analysis based on the above exposure synopsis; nevertheless, public health concerns dictate providing such an analysis.

A unit risk to ambient nickel and nickel compounds based on nickel exposure in the occupational environment can be estimated recognizing that the combination of forms and particulate sizes in the two environments are likely to be qualitatively different. Pedersen et al. (1973), for example, specifically associates the nickel caused nasal sinus cancer with nickel refinery exposure and not to those forms in the general environment. Therefore, separate ambient unit risk estimates for lung cancer and nasal cancer based upon occupational exposures are presented below. Both Doll's and Pedersen's epidemiological studies of nickel workers were used to make quantitative risk assessments, although better estimates of exposure exist for the Doll study.

PEDERSEN

The Pedersen et al. study showed increased but differential risks among different occupational groups, specifically the roasting, smelting, and electrolysis workers. Nickel compounds associated with these processes include nickel sulfide, nickel oxide, nickel chloride, nickel sulfate, and nickel dust. Measurements observed in the early 1970's showed levels averaging from below 0.1 to 0.8 mg/m^3. In determining an exposure estimate for the earlier periods it must be acknowledged that the earlier exposures must have been considerably higher. Determination of an estimate can be based on a modification of the International Nickel Company (INCO) estimates from the Clydach, Wales plant which ranged from 20-50 mg Ni/m^3 between 1902-1930, to 3-50 mg Ni/m^3 in the mid to late 1940's, (INCO, 1976), the higher exposures occurring in the calciner sheds. Because the calciners represent a much higher exposure than what workers would have experienced in Norway, choice of other estimates, ranging from 3-35 mg Ni/m^3, appears to be more suitable. Estimates of unit risk will be based on this range.

The Pedersen study does not record the number of years worked so the estimate is made that exposure lasted for about one quarter of a lifetime.

For the low exposure range, we can estimate an average lifetime exposure for workers as:

$$\text{exposure} = 3\ \text{mg/m}^3 \times \frac{8}{24}\ \text{hrs} \times \frac{240}{365}\ \text{days} \times \frac{1}{4}\ \text{lifetime} \times 10^3\ \mu\text{g/mg}$$

$$= 164\ \mu\text{g/m}^3$$

For the high end of the range, average lifetime exposure is 1918 μg/m^3.

The estimated unit lifetime probability, B_H, of dying from cancer from exposure to these airborne nickel compounds at 1 μg/m^3 over 70 years of continuous exposure is given by:

$$B_H = P_o \frac{(R - 1)}{X_2}$$

where P_o is the lifetime risk of dying from that particular type of cancer for a person living in the United States, R is the relative risk in exposed workers, X_2 is the exposure experienced by the nickel workers usually in μg/m^3 or ppm.

The relative risk estimated for the Norwegian workers in the 1980 update was 3.7 for lung cancer, and 23.9 for nasal sinus cancer. The lifetime probability of death from lung cancer in the general population in the United States is .036 (ICD 161-163, includes larynx) and the probability of death from nasal sinus cancer (ICD 160) is 2.8×10^{-4}.

The estimated lifetime probability of death from lung and larynx cancer from nickel at the rate of 1 μg/m^3 of continuous exposure for 70 years is estimated as:

$B_H = 0.036(2.7)/164 = 5.9 \times 10^{-4}$ for the low exposure estimate and

$B_H = 5.1 \times 10^{-5}$ for the high exposure estimate.

Likewise, the estimated unit lifetime probability of death from nasal sinus cancer from nickel at the rate of 1 μg/m^3 for 70 years of continuous exposure is:

$B_H = 0.00028(23.9)/164 = 4.1 \times 10^{-5}$ for the low exposure estimate and

$B_H = 3.5 \times 10^{-6}$ for the high exposure estimate.

The range of total unit risk from combined lung, larynx and nasal cancer can be estimated by adding the two risks above, as follows:

for the lower limit:

$$B_H = 5.1 \times 10^{-5} + 3.5 \times 10^{-6} = 5.4 \times 10^{-5}$$

and for the upper limit of risk:

$$B_H = 5.9 \times 10^{-4} + 4.1 \times 10^{-5} = 6.3 \times 10^{-4}$$

DOLL

A risk assessment can also be made from the epidemiologic data at Clydach, Wales (Doll et al., 1977). The rates prior to 1930 will be used to calculate the risk assessment, because risk declined dramatically after 1925; this reduction in risk was statistically significant after 1930. As discussed in the epidemiology section, it is believed that the new procedure used after 1925 led to the carcinogen being at least drastically reduced in the environment. INCO estimates that prior to 1930, the concentration of airborne nickel dust in areas of high exposure was 20-50 mg Ni/m^3. Because not all workers were in high risk areas and those who were, probably were exposed for less than 8 hrs/day, we estimate 10 mg Ni/m^3 as the lower bound to the range.

Because the exposure estimate used describes conditions between 1900-1930 only, the fraction of lifetime exposed should reflect exposure before 1930 only. This can be estimated as shown in Table 7-6.

TABLE 7-6. ESTIMATION OF FRACTION OF LIFETIME EXPOSED TO NICKEL IN THE WORKPLACE, CLYDACH, WALES

Period Starting Employment	Number of men	x	Average Number of Years Exposed Prior to 1930	=	Man-years Exposed
1902-1909	119	x	25		2975
1910-1914	150	x	17.5		1875
1915-1919	105	x	12.5		787.5
1920-1924	285	x	7.5		2137.5
1925-1929	103	x	2.5		257.5
Total	762		2.5		8032.5

Source: Adapted from Doll et al. (1977).

Average number of years exposed 8032.5/762 = 10.5 years or 0.15 of 70 year lifetime.

The average lifetime exposure for the workers, X_2, was:

$$X_2 = 10\ \text{mg/m}^3 \times \frac{8}{24}\ \text{hrs} \times \frac{240}{365}\ \text{days} \times 0.15\ \text{lifetime} \times 10^3\ \mu\text{g/mg}$$

$$= 329\ \mu\text{g/m}^3$$

for the low exposure estimate and $X_2 = 1644\ \mu\text{g/m}^3$ for the high exposure estimate.

The relative risk estimated by Doll was 6.2 for lung cancer (ICD 161-163) and 287 for nasal sinus cancer (ICD 160). The lifetime lung cancer risk, P_o, to the general population is approximately 0.036.

The range of estimated lifetime probability of death from lung cancer from nickel at the rate of 1 μg/m^3 for 70 years of continuous exposure is:

$$B_H = \frac{(0.036)\ (5.2)\ (1\ \mu\text{g/m}^3)}{329\ \mu\text{g/m}^3} = 5.7 \times 10^{-4}$$

for the low exposure limit and

$$B_H = 1.1 \times 10^{-4} \text{ for high exposure limit.}$$

The lifetime nasal sinus cancer risk P_o in the general population is approximately 2.8×10^{-4}.

The range of estimated lifetime probability of death from nasal sinus cancer from nickel at the rate of 1 μg/m^3 for 70 years of continuous exposure is:

$$B_H = \frac{(2.8 \times 10^{-4})\ (286)\ (1\ \mu\text{g/m}^3)}{329\ \mu\text{g/m}^3} = 2.4 \times 10^{-4}$$

for the low exposure estimate and $B_H = 4.9 \times 10^{-5}$ for the high exposure estimate.

The range of total unit risk from lung, larynx, and nasal cancer combined can be estimated as before by adding the range of risk as follows:

for the lower limit:

$$B_H = 1.1 \times 10^{-4} + 4.9 \times 10^{-5} = 1.6 \times 10^{-4}$$

and for the upper limit of risk:

$$B_H = 5.7 \times 10^{-4} + 2.4 \times 10^{-4} = 8.1 \times 10^{-4}$$

7.6.6 Comparison of Results

Calculation of risks from both animal and human studies show similar results. Based on 1 μg Ni_3S_2/m^3 over a lifetime, the projected upper limit lifetime unit risk based on data from the Ottolenghi study on Fischer rats is 4.8×10^{-3}. This compared with an upper limit total unit risk to humans from the human data in the Pedersen study of 6.3×10^{-4} and from the human data in the Doll study of 8.1×10^{-4}. If these upper limit risks from the Pedersen and Doll studies are averaged, the geometric mean is

$$[(6.3 \times 10^{-4})\ (8.1 \times 10^{-4})]^{1/2} = 7.1 \times 10^{-4}$$

which is just slightly less than the upper limit risks estimated for the animal studies. A comparison of these human cancer risk estimates with those extrapolated from animal data is presented in Table 7-7.

7.6.7 Relative Potency

One of the uses of unit risk is to compare the potency of carcinogens. To estimate the relative potency on a per mole basis, the unit risk slope factor is multiplied by the molecular weights and the resulting number expressed in terms of $(\mathrm{mMol/kg/day})^{-1}$. This is called the relative potency index.

Figure 7-1 is a histogram representing the frequency distribution of potency indices of 53 chemicals evaluated by the CAG as suspect carcinogens. The actual data summarized by the histogram are presented in Table 7-8. When human data are available for a compound, they have been used to calculate the index. When no human data are available, animal oral studies and animal inhalation studies have been used in that order. Animal oral studies are selected over animal inhalation studies because most of the chemicals have animal oral studies; this allows potency comparisons by route.

The potency index for nickel compounds based on lung cancer in occupational studies by Pedersen and by Doll is $7 \times 10^{+1}$. This is derived as follows: the range of unit risk estimates based on the geometric mean of both studies is $7.5 \times 10^{-5} - 5.8 \times 10^{-4}$ $(\mu g/m^3)^{-1}$ Table 7-7. We first take the midpoint of the range 3.3×10^{-4} $(\mu g/m^3)^{-1}$. This is then converted to units of $(mg/kg/day)^{-1}$, assuming a breathing rate of 20 m^3 of air per day and 70 kg person.

$$3.3 \times 10^{-4} \ (\mu g/m^3)^{-1} \times \frac{1 \text{ day}}{20 \text{ m}^3} \times \frac{1 \ \mu g}{10^{-3} \text{ mg}} \times 70 \text{ kg} = 1.2 \ (mg/kg/day)^{-1}$$

Multiplying by the molecular weight of 58.7 gives a potency index of $7 \times 10^{+1}$. Rounding off to the nearest order of magnitude gives a value of +2 which is the scale presented on the horizontal axis of Figure 7-1. The index of $7 \times 10^{+1}$ lies in about the middle of the third quartile of the 53 substances which the CAG has evaluated as suspect carcinogens.

Ranking of the relative potency indices is subject to the uncertainty of comparing estimates of potency of different chemicals based on different routes of exposure to different species using studies of different quality. Furthermore, all of the indices are based on estimates of low dose risk using linear extrapolation from the observational range. Thus, these indices are not valid to compare potencies in the experimental or observational range if linearity does not exist there. Finally, the index for nickel is subject to the additional uncertainty of not being able to accurately identify the specific nickel compounds in the workplace. Multiplying by the molecular weight of 58.7 based on the nickel ion probably represents an underestimation of the potency.

TABLE /-7. HUMAN CANCER UNIT RISK ESTIMATES FROM NICKEL EXPOSURE

Lifetime Risk of 1 μg Nickel/m^3

	Range of Lung and Larynx Cancer	Range of Nasal Cancer	Range of Total Lung, Larynx and Nasal Cancer
Pedersen	5.1×10^{-5} - 5.9×10^{-4}	3.5×10^{-6} - 4.1×10^{-5}	5.4×10^{-5} - 6.3×10^{-4}
Doll	1.1×10^{-4} - 5.7×10^{-4}	4.9×10^{-5} - 2.4×10^{-4}	1.6×10^{-4} - 8.1×10^{-4}
Geometric Mean	7.5×10^{-5} - 5.8×10^{-4}	1.3×10^{-5} - 9.9×10^{-5}	9.3×10^{-5} - 7.1×10^{-4}
Ottolenghi (Rats)			4.8×10^{-3} (upper limit)

TABLE 7-8. RELATIVE CARCINOGENIC POTENCIES AMONG 53 CHEMICALS EVALUATED BY THE CARCINOGEN ASSESSMENT GROUP AS SUSPECT HUMAN CARCINOGENS[1,2,3]

Compounds	Slope $(mg/kg/day)^{-1}$	Molecular Weight	Potency Index	Order of Magnitude ($\log_{10}$ Index)
Acrylonitrile	0.24(W)	53.1	$1.3\times10^{+1}$	+1
Aflatoxin B_1	2924	312.3	$9\times10^{+5}$	+6
Aldrin	11.4	369.4	$4\times10^{+3}$	+4
Allyl Chloride	1.19×10^{-2}	76.5	9×10^{-1}	0
Arsenic	14(H)	149.8	$2\times10^{+3}$	+3
B[a]P	11.5	252.3	$3\times10^{+3}$	+3
Benzene	5.2×10^{-2}	78	4×10^{0}	+1
Benzidine	234(W)	184.2	$4\times10^{+4}$	+5
Beryllium	4.86	9	$4\times10^{+1}$	+2
Cadmium	6.65(I)	112.4	$7\times10^{+2}$	+3
Carbon Tetrachloride	8.28×10^{-2}	153.8	$1\times10^{+3}$	+3
Chlordane	1.61	409.8	$7\times10^{+2}$	+3
Chlorinated Ethanes				
1,1,2-trichloroethane	5.73×10^{-2}	133.4	8×10^{0}	+1
1,1,2,2-tetrachloroethane	0.20	167.9	$3\times10^{+1}$	+1
Hexachloroethane	1.42×10^{-2}	236.7	3×10^{0}	0
Chloroform	0.11	119.4	$1\times10^{+1}$	+1
Chromium	41	104	$4\times10^{+3}$	+4
DDT	8.42	354.5	$3\times10^{+3}$	+3
Dichlorobenzidine	1.69	253.1	$4\times10^{+2}$	+3
1,1-dichloroethylene	1.04	97	$1\times10^{+2}$	+2
Dieldrin	30.4	380.9	$1\times10^{+4}$	+4

TABLE 7.8 (continued)

Compounds	Slope (mg/kg/day)$^{-1}$	Molecular Weight	Potency Index	Order of Magnitude (log$_{10}$ Index)
Dinitrotoluene	0.31	182	6x10^{+1}	+2
Diphenylhydrazine	0.77	180	1x10^{+2}	+2
Epichlorohydrin	2.4x10^{-2}	92.5	2x10^{0}	0
Bis(2-chloroethyl)ether	1.14	143	2x10^{+2}	+2
Bis(chloromethyl)ether	9300(I)	115	1x10^{+6}	+6
Ehtylene Dibromide (EDB)	8.51	187.9	2x10^{+3}	+3
Ethylene Dichloride (EDC)	5.84x10^{-2}	99.0	6x10^{0}	+1
Ethylene Oxide	0.63(I)	44.0	3x10^{+1}	+1
Formaldehyde	2.14x10^{-2}(I)	30	6x10^{-1}	0
Heptachlor	3.37	373.3	1x10^{+3}	+3
Hexachlorobenzene	1.67	284.4	5x10^{+2}	+3
Hexachlorobutadiene	7.75x10^{-2}	261	2x10^{+1}	+1
Hexachlorocyclohexane				
technical grade	4.75	290.9	1x10^{+3}	+3
alpha isomer	11.12	290.9	3x10^{+3}	+3
beta isomer	1.84	290.9	5x10^{+2}	+3
gamma isomer	1.33	290.9	4x10^{+2}	+3
Nickel	1.15(W)	58.7	7x10^{+1}	+2
Nitrosamines				
Dimethylnitrosamine	25.9(not by q_1^*)	74.1	2x10^{+3}	+3
Diethylnitrosamine	43.5(not by q_1^*)	102.1	4x10^{+3}	+4
Dibutylnitrosamine	5.43	158.2	9x10^{+2}	+3
N-nitrosopyrrolidine	2.13	100.2	2x10^{+2}	+2
N-nitroso-N-ethylurea	32.9	117.1	4x10^{+3}	+4
N-nitroso-N-methylurea	302.6	103.1	3x10^{+4}	+4
N-nitroso-diphenylamine	4.92x10^{-3}	198	1x10^{0}	0
PCBs	4.34	324	1x10^{+3}	+3

TABLE 7.8 (continued)

Compounds	Slope $(mg/kg/day)^{-1}$	Molecular Weight	Potency Index	Order of Magnitude (log_{10} Index)
Phenols 2,4,6-trichlorophenol	1.99×10^{-2}	197.4	4×10^{0}	+1
Tetrachlorodioxin	4.25×10^{5}	322	$1 \times 10^{+8}$	+8
Tetrachloroethylene	5.31×10^{-2}	165.8	9×10^{0}	+1
Toxaphene	1.13	414	$5 \times 10^{+2}$	+3
Trichloroethylene	1.26×10^{-2}	131.4	2×10^{0}	0
Vinyl Chloride	1.75×10^{-2}(I)	62.5	1×10^{0}	0
Vinylidene Chloride	0.13(I)	97	$1 \times 10^{+1}$	+1

Remarks:

1. Animal slopes are 95% upper-limit slopes based on the linear multistage model. They are calculated based on animal oral studies, excpet for those indicated by I (animal inhalation), W (human occupational exposure), and H (human drinking water exposure). Human slopes are point estimate, based on a linear non-threshold model.

2. The potency index is a rounded-off slope in $(mMol/kg/day)^{-1}$ and is calculated by multiplying the slopes in $(mg/kg/day)^{-1}$ by the molecular weight of the compound.

3. Not all the carcinogenic potencies presented in this table represent the same degree of certainty. All are subject to change as new evidence becomes available.

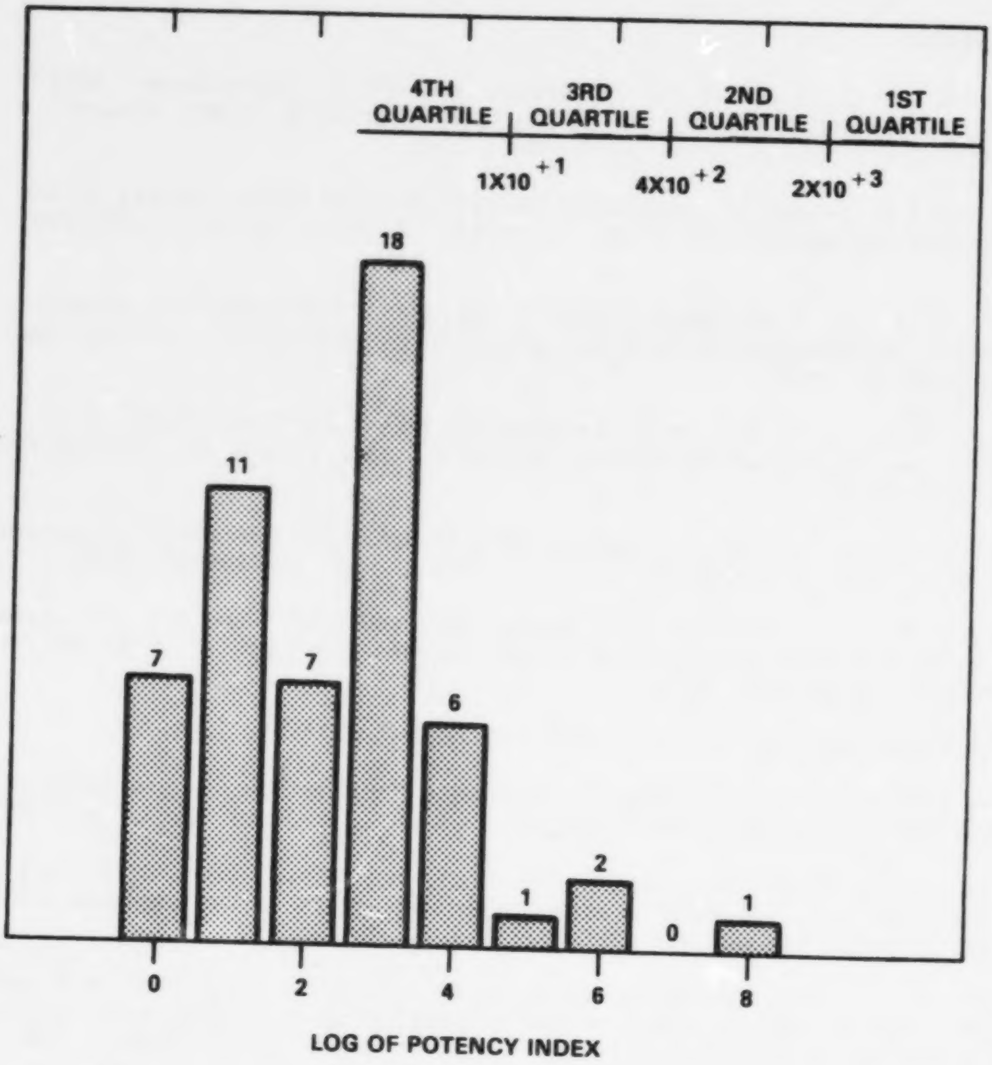

Figure 7-1. Histogram representing the frequency distribution of the potency indices of 53 suspect carcinogens evaluated by the Carcinogen Assessment Group

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